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**LEUKEMIA &
LYMPHOMA
SOCIETY®**

fighting blood cancers

Hodgkin Lymphoma



Zach, Hodgkin lymphoma survivor

The Leukemia & Lymphoma Society wants you to have the most up-to-date information about blood cancer treatment. See below for important new information that was not available at the time this publication was printed.

In August 2015, the Food and Drug Administration (FDA) approved brentuximab vedotin (Adcetris®) for the treatment of patients with classical Hodgkin lymphoma (HL) at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation.

Brentuximab vedotin is also indicated for classical HL after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.

For more information, contact an Information Specialist at (800) 955-4572 or infocenter@lls.org.

A Message From John Walter

President and CEO of The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society (LLS) believes we are living at an extraordinary moment. LLS is committed to bringing you the most up-to-date blood cancer information. We know how important it is for you to have an accurate understanding of your diagnosis, treatment and support options. An important part of our mission is bringing you the latest information about advances in treatment for Hodgkin lymphoma, so you can work with your healthcare team to determine the best options for the best outcomes. Our vision is that one day the great majority of people who have been diagnosed with Hodgkin lymphoma will be cured or will be able to manage their disease with a good quality of life. We hope that the information in this publication will help you along your journey.

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. Since 1954, LLS has been a driving force behind almost every treatment breakthrough for patients with blood cancers, and we have awarded almost \$1 billion to fund blood cancer research. Our commitment to pioneering science has contributed to an unprecedented rise in survival rates for people with many different blood cancers. Until there is a cure, LLS will continue to invest in research, patient support programs and services that improve the quality of life for patients and families.

We wish you well.

A handwritten signature in black ink, appearing to read 'J. Walter', with a large, stylized initial 'J'.

John Walter

President and CEO

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This publication is designed to provide accurate and authoritative information about the subject matter covered. It is distributed as a public service by The Leukemia & Lymphoma Society (LLS), with the understanding that LLS is not engaged in rendering medical or other professional services.

Introduction

Lymphoma is a general name for a group of cancers that affect the lymphatic system. The two major types of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Most forms of HL are highly curable.

In the United States in 2013, about 9,290 persons were expected to be diagnosed with Hodgkin lymphoma. About 172,937 people were living with, or in remission from, HL.

This publication provides detailed information about HL for patients, their families and their caregivers. Brief descriptions of normal blood and marrow and the lymphatic system are provided for background (see page 26). *Hodgkin Lymphoma* also contains information about important considerations before and after treatment to help provide greater quality of life for survivors.

A glossary at the end of the publication can help you understand medical terms. Some of the medical terms used throughout this publication may be synonyms for other words or phrases used by healthcare professionals. Check with your doctor if you have questions about how the terms used in this publication apply to you.

Here to Help

This publication will be helpful when you talk to your doctor about the tests and treatment you need. We encourage you to take the lead in asking questions and discussing your fears and concerns. This will help your healthcare team answer your questions, extend emotional support and provide any needed referrals.

A diagnosis of HL is often a shock to the patient, family members and friends. Denial, depression, hopelessness and fear are some of the reactions people may have. Keep in mind that

- Many people are better able to cope once their treatment plan is established and they can look forward to recovery.
- The outlook for people with HL is continuing to improve. New approaches to therapy are being studied in clinical trials for patients of all ages and at every stage of treatment.

LLS Has Ways to Help. Treatment for HL will affect your daily life, at least for a time. During and after treatment, you may want to have friends, family members or caregivers help you get information. Making treatment choices, paying for medical care, communicating with healthcare providers, family members and friends—these are some of the stressors that go along with a cancer diagnosis. LLS offers free information and patient services for individuals and families touched by blood cancers.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They provide accurate, up-to-date disease and treatment information and are available to speak with callers Monday through Friday, 9 a.m. to 6 p.m. ET at (800) 955-4572. You can email infocenter@LLS.org or chat live at www.LLS.org.

Clinical Trials. Our Information Specialists help patients work with their doctors to find out about specific clinical trials. Information Specialists conduct clinical-trial searches for patients, family members and healthcare professionals. You can also use an online clinical-trial search service supported by LLS that offers patients and caregivers immediate access to listings of blood cancer clinical trials. Please visit www.LLS.org/clinicaltrials.

Advocacy and Public Policy. The LLS Office of Public Policy (OPP) enlists volunteers to help advocate for policies and laws to speed the development of new treatments and improve access to quality medical care. Visit www.LLS.org/advocacy to find out more or get involved.

Co-Pay Assistance Program. This program offers assistance for financially eligible patients with certain blood cancer diagnoses to help pay for private or public health insurance premiums and/or co-pay costs for prescription medications. Check www.LLS.org/copay or call (877) 557-2672 to speak to a Co-Pay Assistance Program specialist for eligibility information.

Language Services. Free language services are available when you speak with an Information Specialist. Let your doctor know if you want a professional healthcare interpreter who speaks your native language or uses sign language to be present during your visit. Many times, this is a free service.

Información en Español. LLS has a number of resources available in Spanish for patients, caregivers and healthcare professionals. You can read and download these resources online at www.LLS.org/espanol or order printed copies by mail or phone.

Free Materials. LLS publishes many free education and support materials for patients and healthcare professionals. PDF files can be read online or downloaded. Free print versions can be ordered. Visit www.LLS.org/resourcecenter.

Chapter Programs and Services. LLS chapter offices around the United States and Canada offer support and education. Your chapter can arrange for peer-to-peer support through the *Patti Robinson Kaufmann First Connection Program*. The *Patient Financial Aid* program offers a limited amount of financial aid for qualified patients. Find your chapter by calling (800) 955-4572 or by visiting www.LLS.org/chapterfind.

Other Helpful Organizations. Our website, www.LLS.org/resourcedirectory, offers an extensive list of resources for patients and families about financial assistance, counseling, transportation, summer camps and other needs.

Telephone/Web Education Programs. LLS provides a number of free, live telephone and web education programs presented by experts for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

Children's Concerns. Each family that receives a diagnosis of childhood HL is thrown into an unfamiliar world of treatment and follow-up care. The child, parents and siblings need support. Help is available. Don't hesitate to ask for assistance for your child, yourself or other family members, even if you are already working with a psychologist, social worker or child life specialist. For practical guidance on how to support your child and other family members, deal with your own concerns, share the news with extended family and friends and make the transition to life after treatment ends, see the free LLS publication *Coping With Childhood Leukemia and Lymphoma*.

Suggestions From Other People Living With Cancer

- Get information about choosing a cancer specialist or treatment center.
- Find out about financial matters: What does your insurance cover? What financial assistance is available to you?
- Learn about the most current tests and treatments for HL.
- Keep all appointments with your doctor and talk openly about your fears or concerns or any side effects you experience.
- Talk with family and friends about how you feel and how they can help.
- Contact your doctor if you have fatigue, fever, pain or sleep problems so that any issues can be addressed early on.
- Get medical advice if you experience changes in mood, feelings of sadness or depression.

Reach Out. You and your loved ones can reach out for support in several ways. For example

- LLS offers online Blood Cancer Discussion Boards as well as online chats at www.LLS.org/getinfo.
- Local or Internet support groups and blogs can provide forums for support.
- Patients with cancer often become acquainted with one another, and these friendships provide support.

Information for Veterans. Veterans with certain blood cancers who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information call the Department of Veterans Affairs at (800) 749-8387 or visit www.publichealth.va.gov/exposures/agentorange.

Information for World Trade Center Survivors. People who were involved in the aftermath of the attacks of September 11, 2001 may be eligible for help from the World Trade Center Health Program. These include: responders, workers and volunteers who helped with rescue, recovery and cleanup at the World Trade Center and related sites in New York City; survivors who were in the New York City disaster area or who lived, worked or were in school in the area; and responders to the Pentagon and the Shanksville, PA crash who have been diagnosed with a blood cancer. For more information, call the World Trade Center Health Program at (888) 982-4748 or visit www.cdc.gov/wtc/faq.html.

Depression. Treatment for depression has proven benefits for people living with cancer. Depression is an illness that should be treated even when a person is undergoing HL treatment. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a two-week period. Contact LLS or ask your healthcare team for guidance and referrals to other sources of help, such as counseling services or community programs. For more information you can contact the National Institute of Mental Health (NIMH) at www.nimh.nih.gov and enter “depression” in the search box at the top of the web page, or call the NIMH toll free at (866) 615-6464.

We’d Like to Hear From You. We hope this publication helps you. Please tell us what you think at www.LLS.org/publicationfeedback. Click on “LLS Disease & Treatment Publications—Survey for Patients, Family and Friends.”

Hodgkin Lymphoma

Hodgkin lymphoma (HL), one of the most curable forms of cancer, was named for Thomas Hodgkin, a British pathologist. In 1832, Dr. Hodgkin described several cases of people with symptoms of a cancer involving the lymph nodes. This disease was called “Hodgkin’s disease” for about 170 years. It was officially renamed “Hodgkin lymphoma” in the late 20th century—when it became evident that the disease results from an injury to the DNA of a lymphocyte (type of white blood cell). The damage to the DNA is acquired (occurs after birth) rather than inherited. The altered DNA in the lymphocyte produces a cancerous change that—if untreated—results in the uncontrolled growth of the cancerous lymphocytes. The accumulation of the cancerous lymphocytes results in the tumor masses that are found in the lymph nodes and other sites in the body (see *Signs and Symptoms* on page 8).

HL is distinguished from other types of lymphoma by the presence of “Reed-Sternberg cells” (named for the scientists who first identified them). Reed-Sternberg cells are usually B cells and have differences and variations to them. The frequency with which these cells are seen and the variations observed help determine a patient’s subtype. Other cells associated with the disease are called “Hodgkin cells.”

Incidence, Causes and Risk Factors

Incidence. HL is most likely to be diagnosed in people in their 20s or early 30s. It is less common in middle age but becomes more common again after age 65 (see Figure 1).

Hodgkin Lymphoma: Age-Specific Incidence Rates 2006-2010

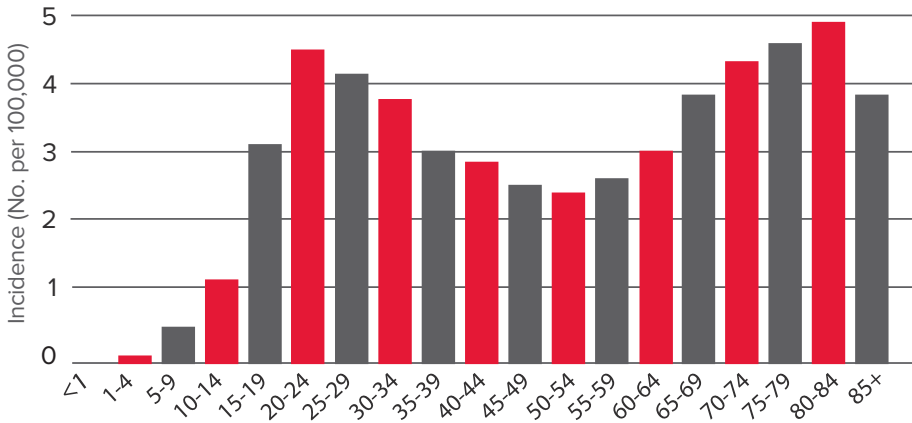


Figure 1. | The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of Hodgkin lymphoma per 100,000 people, by age-group. Incidence of Hodgkin lymphoma peaks at ages 15 to 44 and at age 60 and older (source: Surveillance, Epidemiology and End Results [SEER] Program; National Cancer Institute; 2013)

Causes and Risk Factors. Most cases of HL occur in people who do not have identifiable risk factors; most people with identifiable risk factors do not develop HL. The following are examples of risk factors.

- Patients who have a history of a blood test confirming mononucleosis have a 3-fold increased risk of HL compared to the general population.
- People infected with human T-cell lymphocytotropic virus (HTLV) or human immunodeficiency virus (HIV) also have increased probability of developing HL.
- There are occasional cases of familial clustering, as with many cancers, and there is an increase in the incidence of HL in siblings of patients with the disease. These cases are uncommon, but the concept of genetic predisposition is under study to determine its role in the sporadic occurrence of HL in otherwise healthy individuals. For more information, see “Disease Registries” at www.LLS.org/resourcedirectory under Blood Cancer - General Information or contact our Information Specialists at (800) 955-4572.

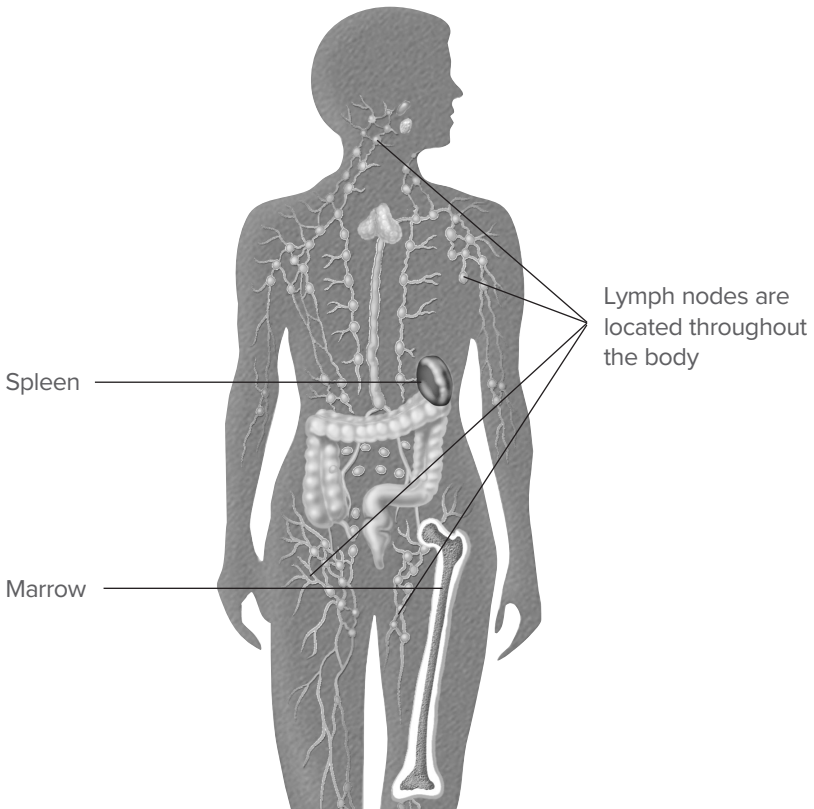
The results of certain studies about causes of HL have not been definitive. For example

- Many studies that link HL and environmental, especially occupational, exposures have been conducted with unclear results.
- Epstein-Barr virus has been associated with nearly half of all cases. However, this virus has not been conclusively established as a cause of HL.

Signs and Symptoms

The most common early sign of HL is a painless swelling (enlargement) of one or more lymph nodes. The vast majority of patients with HL have affected lymph nodes in the upper part of the body—usually in the neck or upper chest. Sometimes the affected lymph node is in the armpit, abdomen or groin. There are about 600 lymph nodes in the body (see Figure 2 below).

Hodgkin Lymphoma and the Lymphatic System



The lymphatic system is part of the immune system. The normal immune system helps to protect the body from infection. The marrow, lymph nodes and spleen are some of the parts of the immune system. There are about 600 lymph nodes throughout the body.

Figure 2. | Lymph nodes and other lymphoid tissues that are commonly involved in lymphoma are those around the ears and jaw, in the tonsils and adenoids, in the front and back of the neck, above and below the collar bone, in the armpit, near the elbow, in the chest, in the abdomen, in the pelvis and in the groin. The spleen contains many clusters of lymphocytes that can become malignant and grow, leading to the enlargement of the spleen. The gut-associated (intestinal) lymph tissue may also be the site of lymphoma development.

Other HL symptoms include

- Fever
- Persistent fatigue
- Persistent cough and shortness of breath (if HL is located in the chest)
- Sweating, especially at night (drenching sweats of the whole body, not just the neck area or chest area)
- Weight loss
- Enlarged spleen
- Itching.

Individuals with HL may experience pain in the lymph nodes after drinking alcohol—this is an uncommon but specific symptom.

Diagnosis

Imaging. A doctor may first order imaging tests (see the discussion on imaging in *Staging* on page 12) when a patient’s medical history and physical examination suggest a possible diagnosis of HL. The imaging test(s) may show enlarged lymph nodes in the chest or abdomen or both. Tumor masses can also occur outside the lymph nodes in lung, bone or other body tissue.

Lymph node biopsy. The diagnosis of HL can be difficult and requires an experienced hematopathologist (a doctor who specializes in diagnosing and interpreting the physical changes caused by diseases of the blood and marrow) to analyze the biopsy slides. HL can be confused with various types of non-Hodgkin lymphoma—since the treatment is different, a precise diagnosis is needed. Keep in mind that another opinion by a second hematopathologist may be necessary if there is any doubt about the diagnosis.

A biopsy of an involved lymph node or other tumor site is needed to confirm the diagnosis of HL. A needle biopsy of the lymph node is usually not sufficient to make a firm diagnosis. The entire lymph node or part of the lymph node is surgically removed so that the hematopathologist has enough tissue to make a firm diagnosis.

Lymph node tissue for biopsy can often be removed using a local anesthetic. Chest or abdominal surgery is occasionally necessary for diagnosis and requires general anesthesia. Newer minimally invasive approaches using a thin, lighted tube called a “laparoscope” permit biopsies within body cavities without major incisions or manipulations.

The hematopathologist prepares a slide from the biopsy specimen by placing the tissue in preservative and staining it with dyes, then examines the cells under a microscope. The distinctive patterns of lymph node changes that are characteristic of HL are visible under the microscope and can help the pathologist categorize the patient's HL into one of several subtypes (see Table 1 on page 11).

Immunophenotyping. A technique called “immunophenotyping” is sometimes used to distinguish HL from other types of lymphoma or other noncancerous conditions. The hematopathologist looks for the presence of Reed-Sternberg and Hodgkin cells to confirm a diagnosis of HL.

Subtypes of Hodgkin Lymphoma

There are two main HL subtypes: classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma (see Table 1 on page 11). About 95 percent of HL patients have the classical subtype. Knowing the patient's subtype is important for making treatment decisions.

Classical Hodgkin Lymphoma. Classical HL can be further subdivided. Four major subtypes have been identified.

- **Nodular Sclerosis.** Nodular sclerosis is the most common subtype, representing about 60 to 70 percent of HL cases. Younger patients are more likely to have this type. It is the most common type in young adults age 15-34 years. The nodes first affected are often those located in the center of the chest (the mediastinum). This subtype is characterized by fibrous tissue, visible under the microscope, among the Hodgkin cells. This tissue forms scars, and sometimes after treatment there can be persistent abnormalities, such as small lumps. These may be benign, consisting of scar tissue (also called “residual fibrosis”) that remains after the disease cells have been eliminated. This form of classical HL is highly curable.
- **Mixed Cellularity.** Mixed cellularity is the second most common subtype. It occurs in about 25 percent of patients and mostly in older patients (55-74 years), children (0-14 years), and those with immune disorders such as AIDS. It is a somewhat more aggressive subtype, although just as curable, as nodular sclerosis HL.
- **Lymphocyte-Depleted.** This subtype occurs in about 4 percent of patients, nearly always in older patients as well as those with HIV. It usually indicates extensive disease with a relatively poor outlook and may be misdiagnosed as non-Hodgkin lymphoma.
- **Lymphocyte-Rich Classical.** This subtype is similar to the nodular lymphocyte-predominant subtype under the microscope but has more clinical characteristics in common with classical HL.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma. The nodular lymphocyte-predominant (NLPHL) subtype occurs in about 5 percent of patients. The cells in NLPHL, known as “lymphocytic” and “histolytic” cells, are different from classic Reed-Sternberg B cells. Patients with this subtype may have no symptoms and are usually diagnosed with very limited disease. It is most common in young men. The NLPHL subtype is indolent (slow-growing) and is associated with long-term survival. However, there is a 3 percent risk that this subtype will transform to non-Hodgkin lymphoma. The treatment is somewhat different from the treatment for other subtypes. See *Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL) Treatment* on page 19.

Table 1. Subtypes of Hodgkin Lymphoma

Classical Hodgkin lymphoma

- Nodular sclerosis Hodgkin lymphoma
- Mixed cellularity Hodgkin lymphoma
- Lymphocyte-depleted Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma

Table 1. | This list includes the designated subtypes of Hodgkin lymphoma classified by The World Health Organization (WHO), which influences disease classification throughout the world.

Staging

Doctors use physical examinations and imaging tests (also called “diagnostic radiology”) to determine the extent of the disease. This is called “staging.” Staging provides important information for treatment planning. The staging system commonly used for HL is the Modified Ann Arbor Staging System.

Physical Examination and Imaging Tests. The physical examination and imaging tests help the doctor evaluate

- The location and distribution of lymph node enlargement
- Whether organs other than lymph nodes are involved
- Whether there are very large masses of tumors in one site or another.

Imaging tests include

- Chest x-ray
- Computed tomography (CT) scan of the chest, abdomen and pelvis
- Magnetic resonance imaging (MRI) in select cases
- [18F] Fluorodeoxyglucose positron emission tomography (FDG-PET) (evaluates the whole body).

In many centers, patients have CT scans of the neck, chest, abdomen and pelvis—all the areas where lymph nodes are present—to see whether there are other areas of disease. The CT scan can also show whether there is involvement of the lungs, liver and other organs, which is information that is helpful in staging (see Table 2 on page 13 and Figure 3 on page 14).

The use of PET or PET-CT scans in managing HL is becoming more common. Currently, PET is widely used for staging and response assessment after completion of therapy. It is used to a lesser extent for assessment of response during therapy. PET cannot replace CT scan or bone marrow biopsy in staging HL. However, it can provide complementary information.

Table 2. Stages and Categories of Hodgkin Lymphoma

- Stage I** Apparent involvement of a single lymph node region or a single organ, such as bone.
- Stage II** Involvement of two or more lymph node regions that are close to each other; for example, all in the neck and chest, or all in the abdomen and on the same side of the diaphragm (a thin muscle below the lungs).
- Stage III** Involvement of several lymph node regions in the neck, chest and abdomen (on both sides of the diaphragm).
- Stage IV** Widespread involvement of lymph nodes on both sides of the diaphragm and in other organs, such as the lungs, liver and bones.

Categories A, B, X and E. The four stages of HL can be divided into categories.

- The A category indicates the absence of fever, exaggerated sweating and weight loss.
- The B category indicates that patients have fever, excessive sweating and weight loss.
- The X category indicates bulky disease (large masses of lymphocytes).
- The E category indicates organs involved outside of the lymph system.

For example, stage IIB indicates that the patient has

- Two lymph node sites near each other with disease involvement (for example, enlarged lymph nodes in the neck and near the collarbone or in the neck and the armpit)
- Fever, excessive sweating and weight loss

Patients in the B category often require more aggressive treatment.

Table 2. | The stage and the presence of symptoms determine whether radiation therapy, chemotherapy or both are recommended for treatment (see Table 3 on page 16).

Hodgkin Lymphoma Stages

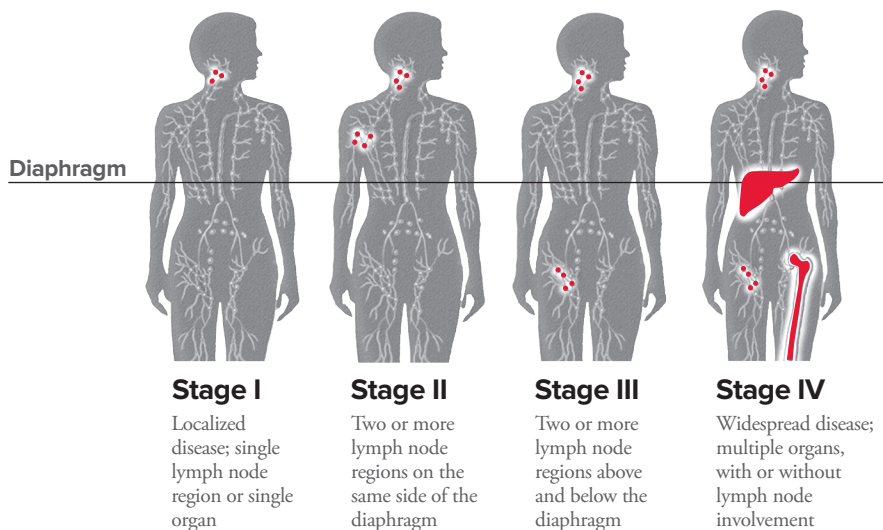


Figure 3. | This illustration shows the location of Hodgkin lymphoma in the body for each stage. The stages are described in Table 2, page 13.

Blood and Bone Marrow Tests. Patients have blood cell counts and other blood tests done to check indicators of disease severity such as blood protein levels, uric acid levels, erythrocyte sedimentation rate (ESR) and liver functions.

Some patients who have been diagnosed with HL may have a bone marrow biopsy. Your doctor will decide if it is necessary to perform depending on certain features such as where the disease is in your body. A bone marrow biopsy may not be required for patients with early-stage disease and low-risk clinical features, such as no symptoms of fever, night sweats, weight loss or bulky disease (large masses of lymphocytes).

Treatment Planning

Treatment for HL is changing due to new drugs and research from clinical trials. Therefore, before treatment begins, it is important to consider getting a second opinion at a center with an HL-specific expert. Additionally, there are continuously updated diagnosis and treatment guidelines published by the National Comprehensive Cancer Network (NCCN) at www.nccn.org, which provide guidance to doctors.

Cure is the goal of treatment for patients with HL. More than 75 percent of all patients diagnosed with HL can be cured by current treatment approaches. The cure rate is higher, approaching 90 percent, in younger patients and those with early stage disease.

Treatment planning factors for HL patients include

- Disease subtype
- Disease stage and category
- Refractory or relapsed disease (if the disease has recurred after treatment)
- Patient age and coexisting diseases or conditions (for example, severe anemia, heart or kidney disease, diabetes).

Clinical trials to identify other prognostic indications for HL patients are under way. See *Research and Clinical Trials* beginning on page 24.

Pretreatment Considerations. Adults of childbearing age and parents of children diagnosed with HL should ask their doctors for information that may lessen the risk for infertility. See the free LLS publication *Fertility* for more details.

Treatment

“Involved field” radiation therapy with chemotherapy (sometimes called “combined modality therapy”) is the most common treatment approach for HL. Involved field radiation therapy targets the evident HL cell masses, and then chemotherapy is used to kill neighboring lymphoma cells.

Radiation therapy consists of the use of special machines that produce high-energy rays capable of killing the HL cells. Continuous improvements in the devices that deliver radiation therapy have led to more precise targeting of treatment areas. In addition, the uninvolved organs, such as the lungs, liver and reproductive organs, are shielded to help minimize the side effects of the treatment.

Chemotherapy may be given without radiation therapy to patients with widespread disease, fever, drenching night sweats and/or weight loss (see Table 3 below).

Chemotherapy usually involves at least four drugs given in combination. The drugs are dissolved in fluid and usually administered to the patient by vein through a peripheral intravenous (IV) line. It is possible that a port, a central line or a percutaneously inserted central venous catheter—known as a “PICC” or a “PIC line”—may be used for some HL patients.

Brentuximab vedotin (Adcetris®), given intravenously (IV), has been FDA-approved for the treatment of HL after failure of autologous stem cell transplant and in HL patients who are not autologous stem cell transplant candidates after failure of at least two multiagent chemotherapy regimens. See www.LLS.org/drugs for more information.

Table 3. Some Treatment Approaches for Hodgkin Lymphoma

- Combination chemotherapy with or without involved field radiation
- Chemotherapy combinations
 - ABVD (Adriamycin® [doxorubicin], bleomycin, vinblastine and dacarbazine)
 - BEACOPP (bleomycin, etoposide, Adriamycin® [doxorubicin], cyclophosphamide, Oncovin® [vincristine], procarbazine and prednisone)
 - Stanford V (mechlorethamine [Mustargen®], doxorubicin, vinblastine, vincristine, bleomycin, etoposide and prednisone)
- High-dose chemotherapy with stem cell transplantation
- Brentuximab vedotin (Adcetris®)

See *Treatment Side Effects* on page 21.

Treatment Setting. Radiation therapy and chemotherapy can be administered in an outpatient clinic of an oncology center. Short periods of hospitalization are sometimes necessary. For example, if therapy is particularly intensive, it may result in prolonged or severe decreases in red blood cell, white blood cell and/or platelet counts. Transfusion of appropriate blood products and administration of blood cell growth factors to enhance blood cell production may be needed. Even in these cases, outpatient treatment may still be feasible. A patient having a stem cell transplant may be treated in an inpatient or an outpatient setting depending on such factors as the transplant center's policies, the type of transplant and the patient's specific medical status.

Stage I and Stage II Hodgkin Lymphoma. The cure rate for patients diagnosed in either stage I or stage II HL exceeds 95 percent. The current treatment approach is to give chemotherapy with reduced amounts of radiation. This approach has resulted in less toxicity and improved outcome. ABVD (Adriamycin® [doxorubicin], bleomycin, vinblastine and dacarbazine) is the most effective and least toxic regimen available to date. ABVD poses less of a risk for leukemia or infertility than other adult combinations.

Current practice guidelines for treatment of early-stage, low-risk HL suggest that about 95 percent of patients can be cured with as few as two courses of ABVD, followed by involved field radiation with a reduced dose of radiation. A recent study has confirmed that this is an effective treatment approach. Results of other clinical trials indicate that chemotherapy alone could benefit the vast majority of patients with stages I and II HL, with about an 85 percent cure rate.

Stages I and II patients with higher risk generally require at least four to six cycles of ABVD, followed by involved field radiation.

See *Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL) Treatment* on page 19 for more information about this subtype.

Advanced Hodgkin Lymphoma. Hodgkin lymphoma is potentially curable in late stages. In general, patients with stage III or IV disease are treated with combination chemotherapy such as six to eight courses of ABVD or escalated BEACOPP (bleomycin, etoposide, Adriamycin® [doxorubicin], cyclophosphamide, Oncovin® [vincristine], procarbazine and prednisone).

Escalated BEACOPP results in a good cure rate but carries a small risk of leukemia or other second cancers. It also has a much higher risk of infertility. For this reason it is a less common treatment in the United States and Canada. It may be used for patients with very aggressive presentations of advanced HL.

International Prognostic Factors for Advanced Hodgkin Lymphoma.

Several years ago an international consortium pooled patient data and identified a prognostic score for advanced HL patients based on seven factors. These factors

provide a basis for recommending either more or less aggressive treatment, including stem cell transplantation, for high-risk patients. The International Prognostic Factors for Advanced HL also promotes uniformity in clinical trial design and evaluation (see Table 4 below).

Table 4. International Prognostic Factors for Advanced Hodgkin Lymphoma

Higher risk is associated with these seven factors—the more factors present, the greater the risk.

The patient is

- Male
- 45 years or older

The patient has

- Stage IV disease
- Hemoglobin of less than 10.5 g/dL
- White blood cell (WBC) count of 15,000/ μ L or higher
- Lymphocyte count less than 600/ μ L and/or less than 8 percent of the total WBC count
- Albumin of less than 4 g/dL

Treatment Response Monitoring. During treatment, patients need to be monitored to check response to therapy. Imaging tests are used to distinguish between tumor and fibrous tissue. FDG-positron emission tomography (FDG-PET) is better than CT scanning in determining that difference.

Posttherapy Surveillance. Periodic examination for recurrence in HL patients is necessary for years after treatment. A patient’s history and physical examination are effective tools for following up with patients. Chest x-rays and CT scans of the chest, abdomen and pelvis are used to detect relapsed disease.

PET scans are useful to see how well the cancer responded to treatment and would be recommended only to establish whether there is a concern for disease recurrence. PET scans are not recommended for ongoing monitoring for disease recurrence. CT scans are more informative.

Patients also need to be monitored for long-term and late effects of treatment. See *Long-Term and Late Effects of Treatment* on page 22.

Relapsed or Refractory Hodgkin Lymphoma. ABVD results in shrinkage of disease in the vast majority of patients. However, some patients have a return of their HL after achieving a remission. This is referred to as “relapse.” For these patients, HL is still potentially curable.

A small percentage of patients have disease that does not respond to initial treatment (called “refractory HL”). Fewer than 10 percent of patients respond only briefly or do not respond to ABVD and experience disease progression. These patients require treatment consisting of high-dose chemotherapy with stem cell transplantation.

Brentuximab vedotin (Adcetris®), given intravenously (IV) has been FDA-approved for relapsed or refractory HL. Adcetris is approved for the treatment of HL after failure of autologous stem cell transplant and in HL patients who are not autologous stem cell transplant candidates after failure of at least two multiagent chemotherapy regimens. See www.LLS.org/drugs for more information.

Stem Cell Transplantation. Stem cell transplantation may provide a cure for some patients with relapsed HL.

Currently, high-dose chemotherapy with stem cell transplantation is not recommended for initial treatment because

- The results of treatment with primary ABVD or BEACOPP are so good.
- High-dose chemotherapy and stem cell transplantation are higher-risk treatments with greater toxicity.

Autologous Stem Cell Transplantation. High-dose chemotherapy with autologous stem cell transplantation is used routinely for many patients in first relapse. With this treatment, disease-free survival rates of 40 to 50 percent are expected at 5 years, and transplant mortality is less than 5 percent.

Allogeneic Stem Cell Transplantation. Some patients who have relapsed many times have been treated successfully with allogeneic stem cell transplantation. However, this treatment has a significant risk of mortality. Other patients may benefit from a reduced-intensity allogeneic transplant, a treatment that uses lower doses of chemotherapy than a standard allogeneic transplant. Data are being collected to compare this treatment to other treatments. Talk to your doctor to find out if stem cell transplantation is a treatment option for you.

See the free LLS publication *Blood and Marrow Stem Cell Transplantation* for more information about autologous and allogeneic stem cell transplants.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)

Treatment. Patients with this subtype of HL need different treatment than patients with classical HL. Almost 80 percent of patients with NLPHL are diagnosed with stage I disease.

This subtype is an indolent (slow-growing) form of HL. It is associated with close-to-100 percent long-term survival, and it is important not to overtreat these patients. At present, the treatment for patients with NLPHL is involved field radiation alone. Although patients do respond to chemotherapy, the disease tends to come back more often after chemotherapy.

Childhood Hodgkin Lymphoma. The incidence of HL in children and young adults under the age of 20 was 1.3 per 100,000 in 2006-2010 (the most recent data available). The 5-year relative survival rate for patients age 15 to 19 years is 97.1 percent. The five-year relative survival rate is 98.1 percent for children and young adults ages 0 to 14 years.

It is important for young adults and parents of children diagnosed with HL to talk to members of the oncology team about the

- Specific subtype of the disease (see page 10)
- Stage of the disease (see page 12)
- Fertility concerns (see *Pretreatment Considerations* on page 15 and 22)
- Other potential risk factors, such as certain laboratory test values
- The rate of response to treatment, which doctors measure using imaging techniques such as PET and PET-CT.

Doctors use this information about the patient's disease to determine the most effective therapy. Doctors are able to develop treatment plans that limit the amount of therapy required to bring about remission. It is important to discuss the planned therapy with members of the oncology team to learn about the drugs, potential side effects and long-term effects and the treatment schedule.

Children and young adults with HL are usually treated with combination chemotherapy, sometimes with the addition of radiation therapy, to increase local control of the disease. The following are some of the combinations that may be used

- COPP (Cytoxan®, Oncovin®, prednisone and procarbazine)
- ABVD (Adriamycin®, bleomycin, vinblastine and dacarbazine)
- COPP-ABV (Cytoxan®, Oncovin®, prednisone and procarbazine, Adriamycin®, bleomycin, and vinblastine)
- CHOP (Cytoxan®, hydroxydaunomycin, Oncovin® and prednisone).

Other combinations including BEACOPP and Stanford V (see Table 3 on page 16) may also be used. The free LLS publication *Understanding Side Effects of Drug Therapy* has useful information about side effects.

Advances in treating childhood HL, which have improved the cure rate and quality of life for survivors, are due in large part to the research of pediatric cooperative groups. The focus of ongoing research and clinical trials is to

- Further improve the cure rate, especially for children with advanced HL such as stages IIIB and IV
- Minimize the risk of long-term and late effects associated with treatment (for example, infertility, impaired cardiac function and second cancers).

Treatment Outcome Summary. Many HL patients are cured after initial treatment. For the smaller number of patients who may have disease recurrence or relapse, additional treatment with chemotherapy, sometimes in combination with stem cell transplantation, is often successful. A large number of these patients are cured or have very prolonged disease-free periods after undergoing a subsequent treatment regimen.

See *Research and Clinical Trials* on page 24 for more information about treatment for all types of Hodgkin lymphoma.

Treatment Side Effects

Infections. One of the important features of HL is a decrease in the immune system's function. The cells of the immune system do not react normally. This situation can make patients susceptible to certain types of infection. Herpes zoster (also known as "shingles") is an example of a viral disease that occurs with increased frequency in patients with HL. Chemotherapy and radiation therapy can make patients more susceptible to infection since these treatments weaken immune cell function. Removal of the spleen, now performed less often, also contributes to the risk of severe infections. However, when patients are cured, their immune function may improve. In addition, improvement in the treatment of patients with HL, increased awareness of the risk of infectious diseases and better antimicrobial therapy have made infectious complications less of a medical problem for patients.

Other side effects depend on the intensity and type of chemotherapy, the location of the radiation therapy, the age of the patient and coexisting medical conditions (diabetes, chronic kidney disease and others). In recent years, new drugs have increased doctors' ability to control nausea, vomiting and other side effects.

HL patients are advised to receive certain vaccinations once they have finished their treatment, including vaccinations for pneumococcal pneumonia and influenza. There are two types of pneumococcal vaccines available for adults: a pneumococcal polysaccharide vaccine (PPSV23) and a pneumococcal conjugate vaccine (PCV13). Immunizations using live organisms or with high viral loads, such as the herpes zoster or shingles vaccine, should not be administered. Your doctor can give you more information.

Suppressed Blood Cell Formation. Blood cell counts can fall in patients treated with chemotherapy, and patients may require blood transfusions. If white blood cell counts drop severely and for extended periods of time, patients may develop infections and require antibiotic treatment. To allow the patient's blood counts to recover from the effects of treatment, their chemotherapy doses or the time between chemotherapy cycles is sometimes altered, or drugs such as granulocyte-colony stimulating factor (G-CSF) are given. See the free LLS publication *Blood Transfusion* for more information.

Effects on Fertility. Patients may be less fertile after treatment. The risk of infertility varies according to the nature of the treatment—the type and amount of chemotherapy, the location of radiation therapy and the patient’s age. Men who are at risk of infertility can consider sperm banking before treatment. Women who have ovarian failure after treatment will experience premature menopause and require hormone replacement therapy. In couples of childbearing age where one partner has received treatment, the incidence of fetal loss and the health of the newborn are very similar to those of healthy couples.

See the free LLS publication *Fertility* for more information.

Other Effects. Treatment may cause nausea, vomiting, diarrhea, extreme fatigue, fever, cough or hair loss. These and other potential effects depend on the drugs and dosages used and on the individual patient’s susceptibility. When side effects do occur, most are temporary and resolve when therapy is completed. Certain drugs have a specific tendency to affect certain tissues (for example, vincristine tends to affect nervous tissue and bleomycin may affect the lungs).

For specific side effect information see the free LLS publication *Understanding Side Effects of Drug Therapy*.

Survivorship

Long-Term and Late Effects of Treatment. Today much is understood about the specific types of treatment for HL and the risk for long-term or late effects, including the risk of developing second cancers. The treatment of HL has changed over the last several years and continues to evolve. Early-stage HL patients are no longer exposed to extended field radiation, reducing the risk of recurrence. ABVD has been used extensively for more than 20 years and it does not pose a significant risk for leukemia or infertility compared to prior therapies. However, there are not as much data on the long-term effects of chemotherapy as there are for the long-term effects of radiation, and further assessment is needed.

Patients who were treated 15 to 20 years ago received aggressive radiation therapy for stage I and II disease. This treatment is associated with long-term and late effects, including a risk for developing a second cancer. The degree of risk for developing a second cancer is related to both the extent and the dosage of radiation treatment. Second cancers, including cancers of the breast, lung, stomach, bone and soft tissues, have been reported as soon as 5 years and as late as 30 years after radiation therapy.

Girls or women below the age of 30 years who have radiation to the breast to treat their HL are at risk for developing breast cancer 15 to 20 years later. Male survivors of childhood cancers may also be at risk for developing second cancers. However, they do not appear to have the same risk for developing breast cancer as female childhood cancer survivors.

Radiation therapy can also injure the lungs, especially when given with bleomycin (the B in ABVD), and survivors who have had chest radiation are also at risk for

developing lung cancer. Smoking further increases their risk. HL survivors are advised not to start smoking or to stop smoking if they do smoke. There is strong scientific evidence that people who do not smoke but received chest radiation for HL 10 to 20 years ago have a risk of lung cancer that is about four times that of the general population. Smokers who were treated for HL with chest radiation may have as much as 25 to 40 times the increased risk of lung cancer, depending on whether they had radiation therapy alone or also had chemotherapy.

Radiation therapy to the chest has also been linked to heart disease, including inflammation of the sac surrounding the heart (pericardium) or myocardial infarction (classic heart attack). Radiation therapy can injure the thyroid gland, causing decreased thyroid function (hypothyroidism).

In the 1970s and 1980s, combination chemotherapy consisting of mechlorethamine, Oncovin® (vincristine), procarbazine and prednisone (MOPP) was used to treat HL. This treatment is associated with an increased risk of leukemia.

Fatigue is a common long-term effect for many people treated for cancer with chemotherapy, radiation therapy or combined modality therapy. For more information, see the free LLS publication *Cancer-Related Fatigue Facts*.

Follow-up Care. Survivors of HL are advised to

- Keep a record of the treatments they received to help the doctors who monitor them for potential health problems after treatment ends.
- Get blood tests every 5 years to measure their cholesterol levels if they were treated with chest radiation.
- Have regular screening for heart disease.
- Have regular screening for cancer. Cancers of the breast, lung, stomach, bone and soft tissues have been reported as soon as 5 years after initial therapy.
- Practice breast self-examination, have early baseline mammograms (within 10 years after therapy or by age 25) and repeat mammograms every two to three years if female and treated with chest radiation for childhood or adult HL. In some cases breast MRI will be recommended. Although some women may develop breast cancer following treatment for HL, it can be detected early and treated, providing the best chance for a cure.
- Have regular lung cancer screening if treated with chest radiation. Smoking further increases the risk of lung cancer and several other types of cancer including acute myeloid leukemia and myelodysplastic syndromes.
- Have regular thyroid function checkups.
- Seek medical and psychosocial support for fatigue, depression and other long-term effects if needed.

For additional information, including risks of specific chemotherapy agents, see the free LLS publications *Long-Term and Late Effects of Treatment in Adults* and *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma*.

Research and Clinical Trials

LLS invests research funds in both basic and applied research programs for HL and other blood cancers. LLS funds research related to immunotherapy and quality of life.

Clinical Trials. Every new drug or treatment regimen goes through a series of studies called “clinical trials” before it becomes part of standard therapy. Clinical trials are carefully designed and rigorously reviewed by expert clinicians and researchers to ensure as much safety and scientific accuracy as possible. Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, available at (800) 955-4572, can offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. Information Specialists can search for clinical trials for patients, family members and healthcare professionals. This service is also available at www.LLS.org/clinicaltrials.

Research Approaches. There are clinical trials for newly diagnosed patients and for patients with relapsed or refractory disease. A number of approaches are under study in clinical trials for the treatment of patients with HL.

Biomarkers and Genetic Causes. Studies are under way to identify biological markers, or “biomarkers,” which are high levels of substances released by cancer cells. Biomarkers can be used to get information about the presence and level of cancer cells. Biomarkers under investigation in HL include interleukin (IL) 10, an immune factor. High levels of IL10 may indicate a relatively poor outlook.

Studies of familial HL are under way to obtain a better understanding of the genetic causes of HL. The goal is to identify genetic changes that may help doctors predict a person’s risk of developing HL.

Interim PET-CT as Decision Tool for Chemotherapy Adjustment. Recent studies comparing different chemotherapy regimens such as ABVD and BEACOPP have led to new challenges to identify clinical or biological prognostic factors that may help doctors recognize those patients who will benefit most from more intensive treatment. Further studies are under way to address the challenges of using PET to assess the benefits of specific therapies (risk-adapted therapies) for individual patients.

Long-term and Late Effects of Treatment. There is considerable interest in studying the use of chemotherapy alone for the treatment of patients with early-stage HL. Several studies have been conducted with results suggesting chemotherapy alone is a viable approach. Studies in this area include

- Comparing outcomes between the use of chemotherapy alone and the use of combined modality therapy (chemotherapy with involved field radiation therapy)
- Collecting and analyzing data on the long-term side effects of ABVD and involved field radiation therapy.

Relapsed or Refractory Hodgkin Lymphoma. Several chemotherapy regimens, with and without targeted therapies, are being studied for effectiveness and safety in advanced, relapsed or refractory disease. Examples of studies include comparisons of outcomes between various combinations of chemotherapy with or without new drugs and antibodies. Adding new agents to chemotherapy regimens may mean that patients can receive reduced amounts of chemotherapy, thereby reducing side effects. Brentuximab vedotin (Adcetris[®]) was FDA approved for relapsed and refractory HL but continues to be studied alone and in combination with traditional chemotherapy drugs. Other agents being studied in relapsed and refractory HL include histone deacetylase inhibitors, such as entinostat, panobinostat, and mocetinostat. Blockage of important pathways involved in HL cell growth is another area of active study. These drugs include PI3-kinase/Akt/mTOR pathway inhibitors, such as everolimus (Afinitor[®]); immune system modulators such as lenalidomide (Revlimid[®]); and chemotherapy drugs such as bendamustine (Treanda[®]).

Quality-of-Life Studies. There are about 172,937 people living with HL in the United States alone. Several studies have described long-term effects of therapy, including second cancers, heart disease and depression, among HL survivors. A great deal is known about the late effects of HL that was diagnosed and treated before 1987. In part, as a result of that knowledge, treatment was changed in the late 1980s to decrease the risk of long-term effects. Investigators are now gathering information on long-term or late effects among survivors who were treated in the past 20 years. The goal is to provide less toxic treatments for people who are diagnosed in the future, while maintaining or improving the cure rates of standard therapy. This information will also be used to propose guidelines for long-term follow-up care for survivors. Study participants may be asked to complete questionnaires about their health and quality of life (such as energy level, outlook on life and any long-term physical effects of the disease).

We encourage you to contact our Information Specialists and visit www.LLS.org for more information about specific treatments under study in clinical trials.

Normal Blood and Marrow and the Lymphatic System

Blood and Marrow. Blood is composed of plasma and cells suspended in plasma. Plasma is largely made up of water in which many chemicals are dissolved. These chemicals include

- Proteins
 - Albumin, the most common protein in blood
 - Blood-clotting proteins, made by the liver
 - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
 - Immunoglobulins, antibodies made by plasma cells in response to infections, including those we develop from our vaccinations (such as poliovirus antibodies, which are made by normal plasma cells in the bone marrow)
- Hormones (such as thyroid hormone and cortisol)
- Minerals (such as iron and magnesium)
- Vitamins (such as folate and vitamin B₁₂)
- Electrolytes (such as calcium, potassium and sodium).

The cells suspended in plasma include red blood cells, platelets and white blood cells (neutrophils, monocytes, eosinophils, basophils, and lymphocytes).

- The red blood cells make up a little less than half the volume of the blood. They are filled with hemoglobin, the protein that picks up oxygen in the lungs and delivers it to the cells all around the body; hemoglobin then picks up carbon dioxide from the body's cells and delivers it back to the lungs, where it is removed when we exhale.
- The platelets are small cells (one-tenth the size of red blood cells) that help stop bleeding at the site of an injury in the body. For example, when a person has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the vessel, clump together, and plug up the bleeding site with the help of blood-clotting proteins such as fibrin and electrolytes such as calcium. Later, a firm clot forms. The vessel wall then heals at the site of the clot and returns to its normal state.
- The neutrophils and monocytes are white blood cells. They are called “phagocytes” (eating cells) because they can ingest bacteria or fungi and kill them. Unlike the red blood cells and platelets, the monocytes can leave the blood and enter the tissue, where they can attack the invading organisms and help combat infection. Eosinophils and basophils are types of white blood cells that respond to allergens or parasites.

- Most lymphocytes, another type of white blood cell, are found in the lymph nodes, the spleen and the lymphatic channels, but some enter the blood. There are three major types of lymphocytes: T lymphocytes (T cells), B lymphocytes (B cells) and natural killer (NK) cells. These cells are a key part of the immune system.

Blood Cell & Lymphocyte Development

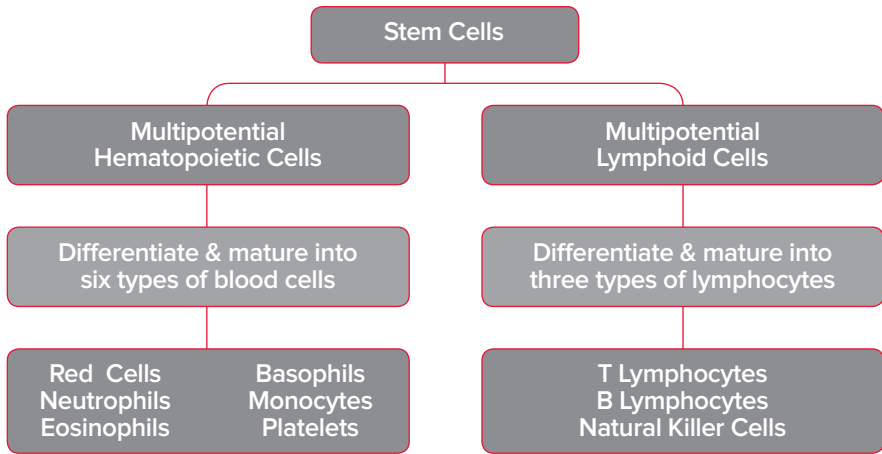


Figure 4. | Stem cells develop into blood cells (hematopoiesis) and lymphoid cells.

Marrow is a spongy tissue where blood cell development takes place. It occupies the central cavity of bones. In newborns, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have functioning marrow. The spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull contain the marrow that makes blood cells in adults. The process of blood cell formation is called “hematopoiesis.” A small group of cells, the stem cells, develop into all the blood cells in the marrow by the process of differentiation (see Figure 4 above).

In healthy individuals, there are enough stem cells to keep producing new blood cells continuously. Blood passes through the marrow and picks up the fully developed and functional red and white blood cells and platelets that will circulate in the blood stream.

Some stem cells enter the blood and circulate. They are present in such small numbers that they cannot be counted or identified by standard blood count tests. Their presence in the blood is important because they can be collected by a special technique. There are also methods to induce more stem cells to leave their home in the marrow and circulate in the blood, allowing a greater number of stem cells to be collected. If enough stem cells are harvested from a compatible donor, they can be transplanted into a recipient.

Stem cell circulation, from marrow to blood and back, also occurs in the fetus. After birth, placental and umbilical cord blood can be collected, stored and used as a source of stem cells for transplantation.

The Lymphatic System. The marrow is really two organs in one. The first is the blood cell-forming organ. The second is the lymphocyte-forming organ and is a part of the immune system.

The marrow produces three main types of lymphocytes. They are

- B lymphocytes (B cells), which make antibodies in response to foreign substances (antigens), especially microbes.
- T lymphocytes (T cells), which mature in the thymus. The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibody attaches to the microbe, making it possible for other white blood cells to recognize the antibody and pull it into the cell along with its attached microbe (ingest it). The white blood cell then kills and digests the microbe.
- Natural killer (NK) cells, which attack virus-infected cells without requiring antibodies or other mediation. T cells and NK cells have other functions as well and are important elements in research efforts to design immunotherapies to treat lymphoma and other cancers.

The lymphocytes circulate through channels called “lymphatics,” which connect the lymph nodes to each other throughout the body. The lymphatic channels collect into large ducts that empty into blood vessels. Lymphocytes enter the blood via these ducts. Most lymphocytes are found in the lymph nodes and other parts of the lymphatic system such as the skin; spleen; tonsils and adenoids (special lymph nodes); intestinal lining; and, in young people, the thymus.

Medical Terms

For longer definitions of words or for definitions of words you do not see in this section, visit www.LLS.org/glossary.

Allogeneic Stem Cell Transplantation. A treatment that uses donor stem cells to restore a patient's marrow and blood cells. A type of allogeneic transplant called a "reduced-intensity" or "nonmyeloablative" transplant is under study. It uses lower doses of conditioning therapy and may be safer, especially for older patients. For more information, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Anemia. A decrease in the number of red blood cells and, therefore, the hemoglobin concentration of the blood. This results in a diminished ability of the blood to carry oxygen. Severe anemia can cause a pale complexion, weakness, fatigue and shortness of breath on exertion.

Antibodies. Proteins released by plasma cells (derived from B lymphocytes) that recognize and bind to specific foreign substances called "antigens." Antibodies coat, mark for destruction or inactivate foreign particles such as bacteria, viruses or harmful toxins.

Antigen. A foreign substance, usually a protein, that stimulates an immune response when it is ingested, inhaled or comes into contact with the skin or mucous membranes. Examples of antigens are bacteria, viruses or allergens. Antigens stimulate plasma cells to produce antibodies.

Antioncogene. See Tumor Suppressor Gene.

Apheresis. The process of removing certain components of a donor's blood and returning the unneeded parts to the donor. The process, also called "hemapheresis," uses continuous circulation of blood from a donor through a specialized machine and then back to the donor. Apheresis makes it possible to remove desired elements from large volumes of blood. Platelets, red blood cells, white blood cells and plasma can be removed separately. See Platelet Transfusion.

Autologous Stem Cell Transplantation. A treatment that uses a patient's own stem cells to delay the progression of certain blood cancers. The autologous transplantation process takes place after the patient achieves a complete response (remission), or a good partial response, to induction drug therapy. For more information, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Biopsy. A procedure to obtain tissue for diagnosis. In many cases, a special needle can be used to obtain the tissue. In some cases, a larger piece of tissue may be surgically removed. Since the appearance of a lymph node is important in categorizing the type of lymphoma that may be present, surgical removal of an entire, swollen lymph node or nodes may be necessary (lymph node biopsy).

Bone Marrow. A spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. In these sites, the marrow is filled with fat cells. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried throughout the body.

Bone Marrow Aspiration. A test to examine marrow cells to detect cell abnormalities. A marrow sample is usually taken from the patient's hip bone. After medication is given to numb the skin, the liquid sample is removed using a special needle inserted through the bone into the bone marrow.

Bone Marrow Biopsy. A test to examine marrow cells to detect cell abnormalities. This test differs from a bone marrow aspiration in that a small amount of bone filled with marrow is removed, usually from the hip (pelvic) bone. After medication is given to numb the skin, a special hollow biopsy needle is used to remove a core of bone containing marrow. Bone marrow aspiration and bone marrow biopsy may be done in the doctor's office or in a hospital. The two tests are almost always done together.

Bone Marrow Transplantation. See Allogeneic Stem Cell Transplantation; Autologous Stem Cell Transplantation.

Central Line (Indwelling Catheter). A special tubing inserted into a large vein in the upper chest. The central line, sometimes referred to as an "indwelling catheter," is tunneled under the skin of the chest to keep it firmly in place. The external end of the catheter can be used to administer medications, fluids or blood products or to withdraw blood samples. See Port.

Chemotherapy. The use of chemicals (drugs or medications) to kill malignant cells. Numerous chemicals have been developed for this purpose, and most act to injure the DNA of the cancer cells. When the DNA is injured, the cells cannot grow or survive.

Chromosome. Threadlike structures within cells that carry genes in a linear order. Human cells have 23 pairs of chromosomes: chromosome pairs 1 to 22 and one pair of sex chromosomes (X for females and Y for males).

Clonal. The designation for a population of cells derived from a single transformed parent cell. Virtually all cancers are derived from a single cell with an injury (mutation) to its DNA and thus are monoclonal. Leukemia, lymphoma and myeloma are examples of clonal cancers; that is, cancers derived from a single abnormal cell.

Colony-Stimulating Factor. See Growth Factor.

Combined Modality Therapy. Two or more types of treatment used alternately or at the same time to treat a patient's disease. For example, chemotherapy with involved field radiation therapy is a combined modality therapy for patients with HL.

Computed Tomography (CT) Scan. A technique for imaging body tissues and organs. X-ray transmissions are converted to detailed images using a computer to synthesize x-ray data. The images are displayed as a cross-section of the body at any level from the head to the feet. A CT scan of the chest, abdomen or pelvis permits detection of an enlarged lymph node, liver or spleen. A CT scan can be used to measure the size of these and other structures during and after treatment.

CT Scan. See Computed Tomography Scan.

Cycle of Treatment. An intensive, clustered period of chemotherapy and/or radiation therapy. The therapy may be given for several days or weeks, and this time period represents one cycle of treatment. The treatment plan may call for two, three or more cycles of treatment.

Cytogenetic Analysis. The process of analyzing the number and size of the chromosomes of cells. It detects chromosome alterations and, in some cases, may identify the actual genes that have been affected. These findings help healthcare professionals diagnose specific types of blood cancers determine treatment approaches and monitor the response to treatment. The individual who prepares and examines the chromosomes and interprets the results is called a "cytogeneticist."

Differentiation. The process by which stem cells develop or mature to possess a specific function. Differentiation of stem cells forms the red blood cells, platelets and white blood cells (neutrophils, monocytes, eosinophils, basophils and lymphocytes). See Hematopoiesis.

DNA. The genetic material in the cell. Deoxyribonucleic acid is the scientific name for DNA, which is made up of a sugar-phosphate backbone with ladderlike "steps" composed of purines and pyrimidines (building blocks of nucleic acids). The sequence of the purines and pyrimidines in the DNA is responsible for passing genetic information to new cells during the process of cell division; for passing genetic information from one generation to the next during reproduction; and for providing the instructions for building proteins, which in turn carry out the major functions of a cell. A mutation is generally a change in or loss of the sequence of the purines or pyrimidines of the DNA. Mutations can lead to cell death, to changes in the way a cell functions or, in some cases, to cancer.

DNA-Gene Chip. See Microarray.

Eosinophil. A type of white blood cell that participates in allergic reactions and helps fight certain parasitic infections.

Erythrocytes. See Red Blood Cells.

Extranodal Lymphoma. Lymphoma that has spread outside the lymph nodes to the organs—the thyroid, lungs, liver, bones, stomach or central nervous system. Doctors adjust their therapeutic approach if organs outside of lymph nodes are involved. If the brain, liver or bones are involved, for example, the treatment approach is likely to target these areas. If lymphoma is found in any of the organs but not in lymph nodes or multiple lymphatic sites, the disease is called a “solitary extranodal lymphoma.”

Flow Cytometry. A test that permits the identification of specific cell types within a sample of cells. The test helps healthcare professionals examine blood cells, marrow cells or cells from a biopsy. One use of flow cytometry is to determine whether a sample of cells is composed of T cells or B cells. This permits the doctor to determine if the leukemia or lymphoma is of the B- or T-cell type.

G-CSF (Granulocyte-Colony Stimulating Factor). See Growth Factor.

Gene Expression Profiling. A research method that uses microarray analysis to identify a combination of genes that are turned off or on in response to a specific condition. A set of genes in a blood or tissue sample can be used to monitor the levels of thousands of genes at once.

Germ-Cell Mutation. See Mutation.

GM-CSF (Granulocyte-Macrophage Colony Stimulating Factor). See Growth Factor.

Granulocyte. A type of white blood cell that has a large number of granules in the cell body. Neutrophils, eosinophils and basophils are types of granulocytes.

Growth Factor. A chemical used to stimulate the production of neutrophils and shorten the period of low neutrophil counts in the blood after chemotherapy. Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are examples of growth factors that are made commercially. GM-CSF can also stimulate monocytes.

Hemapheresis. See Apheresis.

Hematologist. A doctor who specializes in the treatment of blood cell diseases. This person is either an internist who treats adults or a pediatrician who treats children.

Hematopathologist. See Pathologist.

Hematopoiesis. The process of blood cell development in the marrow. The most undeveloped cells in the marrow are stem cells. They start the process of blood cell development. The stem cells begin to develop into young or immature blood cells such as red blood cells or white blood cells of various types. This process is called “differentiation.” The young or immature blood cells then further develop into fully functional blood cells. This process is called “maturation.”

The mature cells leave the marrow, enter the blood and circulate throughout the body. Hematopoiesis is a continuous process that is active normally throughout life. When the marrow is invaded with cancer cells, the constant demand for new blood cells cannot be met, resulting in a severe deficiency in blood cell counts.

HLA. The abbreviation for “human leukocyte antigen(s).” These antigens are proteins on the surface of most tissue cells, and they give an individual his or her unique tissue type. HLA factors are inherited from mother and father, and the greatest chance of having the same HLA type is between siblings. On average, one in four siblings is expected to share the same HLA type. The testing for HLA antigens is referred to as “tissue typing.”

Immunophenotyping. A method that uses the reaction of antibodies with cell antigens to determine a specific type of cell in a sample of blood cells, marrow cells or lymph node cells. The antibodies react with specific antigens on the cell. A tag is attached to an antibody so that it can be detected. The tag can be identified by the laboratory equipment used for the test. As cells carrying their array of antigens are tagged with specific antibodies, they can be identified. Normal lymphocytes may be distinguished from Reed-Sternberg and Hodgkin cells.

Immunotherapy. The term for several treatment approaches used by doctors to harness the body’s immune system to treat lymphoma and other diseases. These therapies include monoclonal antibody therapy, radioimmunotherapy and vaccine therapy.

Monoclonal antibodies are proteins made in the laboratory that either react with or attach to antigens on the target cells. The antibodies are used therapeutically in three ways: as “naked” antibodies (monoclonal antibodies), as antibodies to which radioactive isotopes are attached (radioimmunotherapy), and as antibodies to which toxins are attached (immunotoxins). For more information, see the free LLS publication *Immunotherapy Facts*.

Indwelling Catheter. See Central Line.

Leukocytes. See White Blood Cells.

Leukopenia. A decrease below normal in the concentration of blood leukocytes (white blood cells).

Lymphadenopathy. Enlargement of lymph nodes.

Lymphatic System. The system comprising the lymph nodes, the thymus gland (in the first several decades of life), the lymphatic channels, the lymphatic tissue of the marrow, the gastrointestinal tract, the skin and the spleen, along with the T, B and natural killer (NK) lymphocytes contained in these sites.

Lymph Nodes. Bean-sized structures, that contain large numbers of lymphocytes and are connected with each other by small channels called “lymphatics.” These nodes are distributed throughout the body. In patients with lymphoma and some types of lymphocytic leukemia, the malignant lymphocytes grow and the lymph nodes may become enlarged. This enlargement of lymph nodes can be seen, felt or measured by computed tomography (CT) scan or magnetic resonance imaging (MRI), depending on the degree of enlargement and the location.

Lymphocyte. A type of white blood cell that is the essential cell type in the body’s immune system. There are three major types of lymphocytes: B lymphocytes, which produce antibodies to help combat infectious agents like bacteria, viruses and fungi; T lymphocytes, which have several functions, including assisting B lymphocytes to make antibodies; and natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Macrophage. See Monocyte/Macrophage.

Magnetic Resonance Imaging (MRI). A testing technique that provides detailed images of body structures. It differs from the CT scan in that the patient is not exposed to x-rays. Signals are generated in the tissues in response to a magnetic field produced by a specialized instrument and are converted by computer into images of body structures. Healthcare professionals use MRI to measure the size, or a change in size, of organs such as the lymph nodes, liver and spleen or tumor masses.

Marrow. See Bone Marrow.

Maturation. See Hematopoiesis.

Microarray. A two-dimensional grid of molecules (often but not always DNA genes or gene fragment spots), usually arranged on a glass slide or silicone wafer. A typical microarray (also called “DNA-gene chip”) contains 10,000 to 200,000 microscopic DNA spots. Scientists use a microarray to study gene expression and to learn which genes are expressed or not expressed under given circumstances. See Gene Expression Profiling.

Monoclonal. See Clonal.

Monoclonal Antibody Therapy. See Immunotherapy.

Monocyte/Macrophage. A type of white blood cell that represents about 5 to 10 percent of the cells in normal human blood. The monocyte and the neutrophil are the two major microbe-eating and microbe-killing cells in the blood. When monocytes leave the blood and enter the tissue, they are converted to macrophages. The macrophage is the monocyte-in-action: It can combat infection in the tissues, ingest dead cells (in this function it is called a “scavenger cell”) and assist lymphocytes in their immune functions.

MRI. See Magnetic Resonance Imaging.

Mutation. An alteration in a gene that results from a change to a part of the stretch of DNA that represents the gene. A “germ cell mutation” is present in the egg or the sperm and can be transmitted from parent to offspring. A “somatic mutation” occurs in a specific tissue cell and can result in the growth of that cell into a tumor. Most cancers start after a somatic mutation. In leukemia, lymphoma or myeloma, a primitive marrow (blood-forming) or lymph node cell undergoes a somatic mutation or mutations that lead to the formation of a tumor. If a mutation results from a major abnormality of chromosomes such as a translocation, it can be detected by cytogenetic examination. Sometimes the alteration in the gene is more subtle and requires more sensitive tests to identify the oncogene.

Neutropenia. A decrease below normal in the concentration of neutrophils, a type of white blood cell.

Neutrophil. The principal phagocyte (microbe-eating cell) in the blood. The neutrophil is the main cell that combats infections. Patients with certain blood cancers or patients who have undergone chemotherapy often do not have sufficient quantities of neutrophils circulating in their bloodstream. A severe deficiency of neutrophils increases the patient’s susceptibility to infection.

Nonmyeloablative Stem Cell Transplantation. See Reduced-Intensity Stem Cell Transplantation.

Oncogene. A mutated gene that is the cause of a cancer. Several subtypes of acute myeloid leukemia, acute lymphoblastic leukemia, lymphoma and nearly all cases of chronic myeloid leukemia are associated with an oncogene.

Oncologist. A doctor who diagnoses and treats patients with cancer. Oncologists are usually internists who undergo additional specialized training to treat adults with cancer (or pediatricians, who treat children). Radiation oncologists specialize in the use of radiation to treat cancer, and surgical oncologists specialize in the use of surgical procedures to diagnose and treat cancer. These doctors cooperate and collaborate to provide the best treatment plan (surgery, radiation therapy, chemotherapy or immunotherapy) for the patient.

Pathologist. A doctor who identifies disease by studying tissues under a microscope. A hematopathologist is a type of pathologist who studies diseases of blood cells by looking at peripheral blood smears, bone marrow aspirates and biopsies, lymph nodes and other tissues and uses his or her expertise to identify diseases such as HL. In addition to the microscope, a hematopathologist also uses laboratory values, flow cytometry and molecular diagnostic tests to make the most accurate diagnosis. The hematopathologist works closely with the hematologist or oncologist who sees the patient and decides on the best treatment based upon the diagnosis.

Percutaneously Inserted Central Venous Catheter (PICC or PIC Line). A long, thin, flexible tube that is inserted into the body. It can be left in place for weeks or even months for administration of medications, fluids and nutrition. It can also be used to obtain blood samples. The PICC eliminates the need for standard intravenous (IV) administration.

Phagocytes. Cells that protect the body from infection by eating and killing microorganisms such as bacteria and fungi. The two principal phagocytes are neutrophils and monocytes. They leave the blood and enter tissues in which an infection has developed. Chemotherapy and radiation can cause a severe decrease in the concentrations of these cells which makes patients more susceptible to infection. Treatment may suppress blood cell production in the marrow, resulting in deficiencies of these phagocytic cells.

PICC or PIC line. See Percutaneously Inserted Central Venous Catheter.

Platelets. Small blood cells (about one-tenth the volume of red blood cells) that stick to the site of blood vessel injury, cluster and then seal off the injured blood vessel to stop bleeding. “Thrombocyte” is a synonym for platelet and is often used as the prefix in terms describing disorders of platelets, such as thrombocytopenia (too few) or thrombocythemia (too many).

Platelet Transfusion. Transfusion of donor platelets that may be needed to support some patients treated for HL. The platelets can be collected from several unrelated donors and given as pooled, random-donor platelets. The platelets from about six single-unit blood donors are required to significantly raise the platelet count in a recipient. Sufficient platelets can be obtained from one donor by a procedure known as “apheresis.” Platelets are skimmed from large volumes of blood passing through a specialized machine. The red blood cells and plasma are returned to the donor. The advantage of single-donor platelets is that the patient is not exposed to the different antigens on platelets from many different people and is thus less likely to develop antibodies against donor platelets. HLA-matched platelet transfusion can be given from a related donor who has an identical or very similar HLA tissue type. See the free LLS publication *Blood Transfusion*.

Port. A small device used with a central line (indwelling catheter) to access a vein. The port is placed under the skin of the chest. After the site heals, no dressings or any special home care is required. To give medicines or nutrition or to take blood samples, the doctor or nurse inserts a needle through the skin into the port. A numbing cream can be put on the skin before the port is used.

Positron Emission Tomography (PET) Scan. A procedure used to image lymphoma masses. In this technique, glucose, a type of sugar, is labeled with a positron particle emitting a radioisotope such as fluorine-18. The utilization of sugar is greater in lymphoma cells than in normal tissue, and the isotope thus becomes concentrated in areas of lymphoma. The location of the lymphoma sites in the body can be identified by scanning for intense positron particle emission. PET is combined with CT to establish the precise location of lymphoma masses;

compared to other imaging procedures, PET can detect much smaller lymphoma masses. In some cases, successfully treated lymphoma may convert to fibrous tissue that looks like a mass in imaging studies, perhaps leading the doctor to think that the mass was not successfully treated. Since lymphoma tissue is not fibrous and scars (primarily fibrous) do not take up the fluorine-18-labeled sugar, PET can distinguish residual lymphoma from healed scar tissue. PET is increasingly used for both staging of lymphoma and assessing response.

Radiation Therapy. The use of x-rays and other forms of radiation in treatment. Radiation therapy may be useful in the treatment of localized lymphomas. Radiation therapy can be an important adjunct to therapy when there are particularly large masses of lymphoma in a localized area or when local large lymph nodes are compressing or invading normal organs or structures and chemotherapy cannot control the problem.

Radioactive Isotope. A form of a molecule that emits radiation. Certain types of radiation can damage cancer cells. Doctors use radioactive isotopes to treat cancer in several ways, including attaching the isotope to antibodies. The antibodies can attach to the cancer cell and the radiation can destroy it.

Recurrence/Relapse. The return of a disease after it has been in remission following treatment.

Red Blood Cells. Blood cells (erythrocytes) that carry hemoglobin, which binds oxygen and carries it to the tissues of the body. The red blood cells make up about 40 to 45 percent of the volume of the blood in healthy individuals.

Reduced-Intensity Stem Cell Transplantation. A form of allogeneic transplantation. In reduced-intensity transplantation (also called “nonmyeloablative stem cell transplantation”), patients receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. For more information about all types of stem cell transplantation, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Remission. A disappearance of evidence of a disease, usually as a result of treatment. The terms “complete” and “partial” are used to modify the term “remission.” Complete remission means that all evidence of the disease is gone. Partial remission means that the disease is markedly improved by treatment, but residual evidence of the disease is present. Long-term benefit usually requires a complete remission, especially in progressive lymphomas.

Scavenger Cell. See Monocyte/Macrophage.

Sedimentation Rate. A blood test that measures how quickly red blood cells (erythrocytes) settle in a test tube in one hour. A sedimentation rate test is done to find out if inflammation is present in the body, to check on the progress of a disease or to see how well a treatment is working. This test is also called a “sed rate” or “erythrocyte sedimentation rate (ESR).”

Somatic Mutation. See Mutation.

Spleen. An organ located in the left upper portion of the abdomen just under the left side of the diaphragm. It contains clusters of lymphocytes and also filters old or worn-out cells from the blood. It is often affected in lymphocytic leukemias and lymphomas. Enlargement of the spleen is called “splenomegaly.” Surgical removal of the spleen is known as “splenectomy.”

Stem Cells. Primitive cells in marrow that are essential to the formation of red blood cells, white blood cells and platelets. Stem cells are largely found in the marrow, but some leave the marrow and circulate in the blood. Using special techniques, the stem cells in blood can be collected, preserved by freezing and later thawed and used for stem cell therapy. See Hematopoiesis.

Thrombocyte. See Platelets.

Thrombocytopenia. A decrease below normal in the concentration of platelets in the blood.

Toxin. A naturally derived substance that is poisonous to cells. A toxin can be attached to antibodies that then attach to cancer cells. The toxin may kill the cancer cells.

Translocation. An abnormality of chromosomes in marrow or lymph node cells that occurs when a piece of one chromosome breaks off and attaches to the end of another chromosome. In a balanced translocation, genetic material is exchanged between two different chromosomes with no gain or loss of genetic information. When a translocation takes place, the gene at which the break occurs is altered. This is one form of somatic mutation that may transform the gene into an oncogene (cancer-causing gene). See Mutation.

Tumor Suppressor Gene. A gene that acts to prevent cell growth. If a mutation occurs that “turns off” this gene and causes loss of function, it may make the individual more susceptible to the development of cancer in the tissue in which the mutation occurred. Another term for tumor suppressor gene is “antioncogene.”

White Blood Cells. Any of the five major types of infection-fighting white blood cells in the blood: neutrophils, eosinophils, basophils, monocytes and lymphocytes. White blood cells are also called “leukocytes.”

More Information

Free LLS publications include

Blood and Marrow Stem Cell Transplantation

Blood Transfusion

Cancer-Related Fatigue Facts

Fertility Facts

Understanding Clinical Trials for Blood Cancers

Understanding Side Effects of Drug Therapy

Visit “Suggested Reading” at www.LLS.org/resourcecenter to see a list of helpful books on a wide range of topics.

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