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fighting blood cancers

Chronic Lymphocytic Leukemia

June, CLL survivor

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Revised **2014**

A Message from Louis J. DeGennaro, PhD

President and CEO of The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society (LLS) is the world's largest voluntary health organization dedicated to finding cures for blood cancer patients. Our research grants have funded many of today's most promising advances; we are the leading source of free blood cancer information, education and support; and we advocate for blood cancer patients and their families, helping to ensure they have access to quality, affordable and coordinated care.

Since 1954, we have been a driving force behind almost every treatment breakthrough for blood cancer patients. We have invested more than $1 billion in research to advance therapies and save lives. Thanks to research and access to better treatments, survival rates for many blood cancer patients have doubled, tripled and even quadrupled.

Yet we are far from done.

Until there is a cure for cancer, we will continue to work hard—to fund new research, to create new patient programs and services, and to share information and resources about blood cancers.

This booklet has information that can help you understand chronic lymphocytic leukemia (CLL), prepare your questions, find answers and resources, and communicate better with members of your healthcare team.

Our vision is that, one day, all people with CLL will either be cured or will be able to manage their disease so that they can experience a great quality of life. Today, we hope our expertise, knowledge and resources will make a difference in your journey.

Louis J. DeGennaro, PhD
President and Chief Executive Officer
The Leukemia & Lymphoma Society

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Acknowledgement

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John C. Byrd, MD
D. Warren Brown Chair of Leukemia Research
Professor of Medicine, Medicinal Chemistry and Veterinary Biosciences
Director, Division of Hematology, Department of Internal Medicine
The Ohio State University
Columbus, OH

Introduction

In 2013, an estimated 119,386 people in the United States were living with chronic lymphocytic leukemia (CLL) a disease of the blood and marrow.[1] An estimated 15,720 people were expected to be diagnosed with CLL in 2014. Doctors have learned a great deal in the last few decades about CLL. In the last several years, new therapies have been developed, and outcomes for people living with CLL are steadily improving. Researchers around the world continue to strive to find a cure for CLL.

At LLS, we know that the more you know about your disease, the better you can take care of yourself, your mind and body, and your health.

This booklet provides information about CLL; defines often hard-to-understand terms; explains tests and treatments you may encounter; and lists new research options and clinical trials. Brief descriptions of normal blood and marrow, the lymphatic system and definitions of health terms are included.

We trust this information will provide a good working knowledge base and that it will reinforce what you already know. We hope you keep this booklet handy and, should you ever feel alone confronting problems, we hope you will turn to it for information and guidance, locating the support and resources you need.

We are here to help.

[1]Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD, www.seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, April 2013.

Resources and Information

LLS offers free information and services to patients and families touched by blood cancers. This section of the booklet lists various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team members' knowledge and skills.

For Help and Information

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (Monday through Friday, 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org

- Live chat: www.LLS.org
- Visit: www.LLS.org/informationspecialists.

Free Materials. LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered. For more information, please visit www.LLS.org/publications.

Telephone/Web Education Programs. LLS offers free telephone/Web education programs for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for eligible patients. For more information, please

- Call: (877) 557-2672
- Visit: www.LLS.org/copay.

Community Resources and Networking

Online Blood Cancer Discussion Boards and Chats. Online discussion boards and moderated online chats can provide support and help cancer patients to reach out and share information. For more information, please visit www.LLS.org/getinfo.

LLS Chapters. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your chapter, please

- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind.

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, locating summer camps and other needs. For more information, please visit www.LLS.org/resourcedirectory.

Clinical Trials (Research Studies). New treatments for patients with CLL are under way. Patients can learn about clinical trials and how to access them. For more information, please

- Call: (800) 955-4572 to speak with an LLS Information Specialist who can help conduct clinical-trial searches
- Visit: www.LLS.org/clinicaltrials and click on TrialCheck®.

Advocacy. The LLS Office of Public Policy (OPP) enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy.

Additional Help for Specific Populations

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/espanol.

Language Services. Let your doctor know if you need a language interpreter or other resource, such as a sign language interpreter. Often, these services are free.

Information for Veterans. Veterans with CLL 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 please

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/agentorange.

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area, lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA crashes.

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html.

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a two-week period. For more information, please

- Call: National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov. Enter “depression” in the search box.

Feedback. Like this booklet? Have suggestions? We'd love to know what you think. To tell us

- Visit: www.LLS.org/publicationfeedback
  - Click on "LLS Disease & Treatment Publications—Survey for Patients, Family and Friends."

Leukemia

Leukemia is a cancer of the marrow and blood. The four major types of leukemia are chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and acute myeloid leukemia (AML).

Leukemia is called "lymphocytic" (or "lymphoblastic") if the cancerous change takes place in a type of marrow cell that forms lymphocytes (a type of white blood cell). Leukemia is called "myelogenous" (or "myeloid") if the cell change takes place in a type of marrow cell that would normally go on to form red blood cells, some kinds of white blood cells and platelets.

Acute leukemia is a more quickly growing disease that affects unformed cells or cells that are not yet fully developed. These immature cells cannot carry out their normal functions. Chronic leukemia is a slow-growing blood cancer that permits the growth of greater numbers of more developed cells. In general, these more mature cells can carry out some of their normal functions.

The four main types of leukemia are further classified into subtypes that are based on specific features of cells. Knowing the subtype of the patient's disease may help the doctor to assess how quickly the disease may progress. The subtype is important because the treatment approach may vary according to the disease subtype.

Lymphocytic Leukemia and Lymphoma. The World Health Organization (WHO) includes "lymphocytic leukemias" and "lymphoma" within one classification. Each of these cancers is the result of a change to a cell that was destined to be a lymphocyte. However, lymphocytic leukemia and lymphoma originate in different parts of the body. Lymphocytic leukemia develops in the lymphatic tissue within the bone marrow. Lymphoma begins in a lymph node, or another lymphatic structure in the skin, the gastrointestinal tract, or some other site in the body.

Chronic lymphocytic leukemia (CLL) and small cell lymphocytic lymphoma (SLL) are often considered to be one disease because they are similar with regard to incidence, signs and symptoms, genetic features, disease progression and treatment. The leukemic lymphocytes and tissue abnormalities that are observed in people with SLL are identical to those observed in patients with CLL. However, in people with

SLL, there is more lymph node and lymphoid tissue involvement and less marrow and blood involvement; in people with CLL, the marrow and blood are more affected. Talk to your doctor if you have questions about your specific diagnosis and treatment.

More information about leukemia and lymphoma can be found in the free LLS publications *Understanding Leukemia, The Lymphoma Guide—Information for Patients and Caregivers* and *Non-Hodgkin Lymphoma*.

What is CLL?

Chronic lymphocytic leukemia (CLL) results from an acquired (not present at birth) mutation (change) to the DNA of a single marrow cell that develops into a lymphocyte.

In 95 percent of people with CLL, the change occurs in a B lymphocyte. In the other 5 percent of people with CLL, the cell that transforms from normal to leukemic has the features of a T lymphocyte or a natural killer (NK) cell. Thus, any of the three major types of lymphocytes (T cells, B cells or NK cells) can undergo a malignant transformation that causes diseases related to B-cell CLL (see *Related Diseases* on page 30).

Scientists do not yet understand what causes this change. Once the marrow cell undergoes the leukemic change, it multiplies into many cells. CLL cells grow and survive better than normal cells; over time, they crowd out normal cells.

The result is the uncontrolled growth of CLL cells in the marrow, leading to an increase in the number of CLL cells in the blood. The leukemic cells that accumulate in the marrow in people with CLL do not prevent normal blood cell production as extensively as is the case with acute lymphoblastic leukemia. This is an important distinction: It is the reason for the generally less severe early course of CLL.

CLL takes different forms. Some people have disease that is slow growing. People with minimal changes in their blood cell counts (an increase in the number of blood lymphocytes and little or no decrease in the number of red blood cells, normal neutrophil and platelet counts) may have stable disease for years. Other people with CLL have a faster-growing form of the disease—the CLL cells accumulate in the bone marrow and blood, and there is a significant decrease in the numbers of red blood cells and platelets.

People with faster-growing CLL may have

- Enlarged lymph nodes that can lead to compression of neighboring organs. For example, enlarged lymph nodes in the abdomen can interfere with the functions of the gastrointestinal tract and/or the urinary tract.

- A severe immunoglobulin deficiency, sometimes coupled with a low neutrophil count, which can lead to recurrent infections.
- An enlarged spleen which can press on the stomach causing early fullness (satiety) while eating food and also discomfort in the left upper part of the abdomen.

Causes and Risk Factors. CLL has generally not been associated with any environmental or external factors. However, the Institute of Medicine of the National Academy of Sciences issued a report "Veterans and Agent Orange: Update 2002," which concluded that there was "sufficient evidence of an association" between herbicides used in Vietnam and CLL. For Veterans with Agent Orange exposure, this may provide additional VA benefits. If you fall into this group of patients, it is worth getting a formal evaluation at the VA.

First-degree relatives of patients with CLL are three to four times more likely to develop CLL than people who do not have first-degree relatives with the disease. However, the risk is still small. For example, the 60-year-old sibling or child of someone with CLL would have three to four chances in 10,000 of developing the disease, compared with the one chance in 10,000 for a 60-year-old person without a family history of the disease.

For information on studies about two or more relatives with a hematologic malignancy, please visit www.LLS.org/diseaseregistries.

Incidence. CLL is more common in people who are 70 years and older (see Figure 1 on page 8). The incidence of the disease increases from less than one per 100,000 in individuals aged 40 to 44 years to more than 30 per 100,000 in individuals aged 80 and older. Older patients tend to have a worse outcome due to being diagnosed with a more aggressive CLL and the inability to tolerate treatment and symptoms of the disease.

Chronic Lymphocytic Leukemia: Age-Specific Incidence Rates (2007-2011)

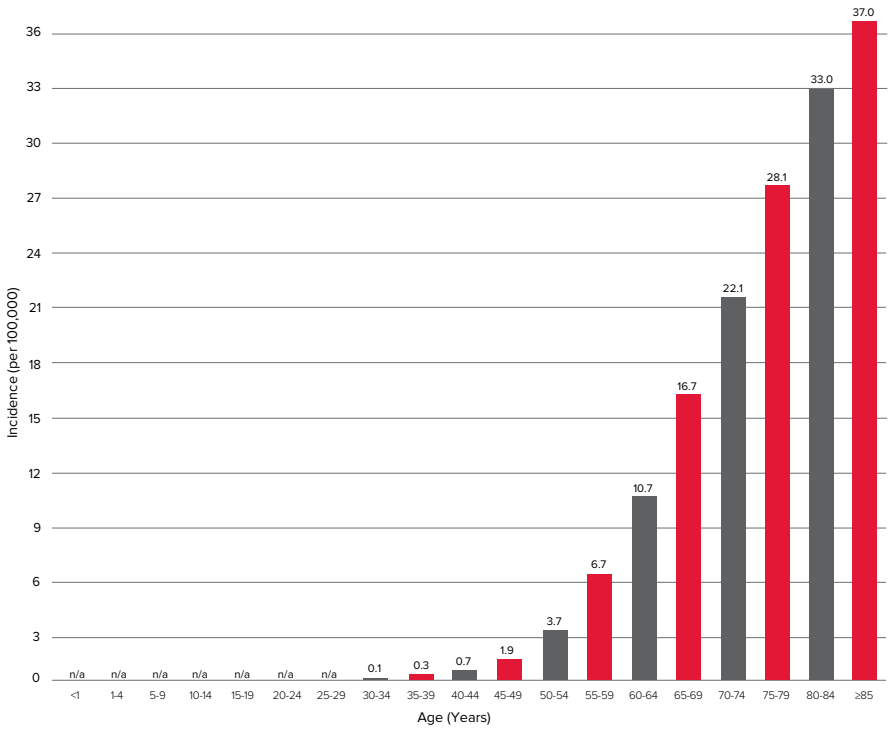

Figure 1. | The horizontal axis shows five-year age intervals. The vertical axis shows the frequency of new cases of CLL per 100,000 people, by age-group. (source: Surveillance, Epidemiology and End Results [SEER] Program; National Cancer Institute; 2014)

Signs and Symptoms

CLL symptoms usually develop over time. Early in the course of the disease, CLL often has little effect on a person's well-being. Some people with CLL do not have any symptoms. The disease may be suspected because of abnormal results from blood tests that were ordered either as part of an annual physical or a medical examination for an unrelated condition. An unexplained elevated white blood cell (lymphocyte) count is the most common finding that leads a doctor to consider a CLL diagnosis.

People with CLL who do have symptoms may

- Tire more easily, and/or feel short of breath during day-to-day physical activities—as a result of anemia (low red blood cell count)
- Lose weight because of decreased appetite and/or increased use of energy

- Have lymph nodes and a spleen that may become enlarged as a result of an accumulation of CLL cells (leukemic lymphocytes)
- Have infections of the skin, lungs, kidneys or other sites that may occur as result of low immunoglobulin levels and decreased neutrophil counts.

Diagnosis

Blood Cell Count and Examination. The diagnosis of CLL is usually evident from the results of blood cell counts and an examination of blood cells. A person with CLL will have increased numbers of lymphocytes. Low platelet counts and low red blood cell counts may also be present; these counts are usually only slightly decreased in the early stage of the illness.

Bone Marrow Examination. A bone marrow aspiration and biopsy generally are not needed to make a diagnosis of CLL provided the red blood cells and platelets are normal. However, these tests are recommended before treatment begins—the test results provide baseline data that can rule out other diseases. They can also be used later on to evaluate the effects of therapy. Repeat marrow biopsies are helpful in distinguishing disease versus treatment-related causes of low blood cell counts that do not improve within an expected period of time after treatment.

In people with CLL, a bone marrow examination will show an increase in the number of lymphocytes in the marrow and often a decrease in the number of normal marrow cells. The bone marrow biopsy results will also show one of four patterns characteristic of CLL: nodular, interstitial, mixed or diffuse.

Immunophenotyping. "Immunophenotyping" (or flow cytometry) of lymphocytes is an important process used to diagnose CLL, and other types of leukemia and lymphoma, by comparing the cancer cells to normal immune cells. The test results indicate whether or not the person's lymphocytes are derived from a single cancer cell (leukemia) or from other conditions in adults that can, infrequently, cause an increase in the number of blood lymphocytes from a noncancerous origin. This test is especially important if the number of lymphocytes in the blood is only slightly elevated. Immunophenotyping also determines whether the CLL cells are from a change in either B-cell or T-cell development (see Figure 2 on page 10). Most people with CLL have the B-cell type.

Immunophenotyping is done with an instrument called a "flow cytometer." A sample of cells from blood or marrow can be tagged with an antibody that is specific for a site on the cell surface. The cells go through the flow cytometer, passing through a laser beam; if they have the antibody-specific surface feature, the cells light up and these cells are counted.

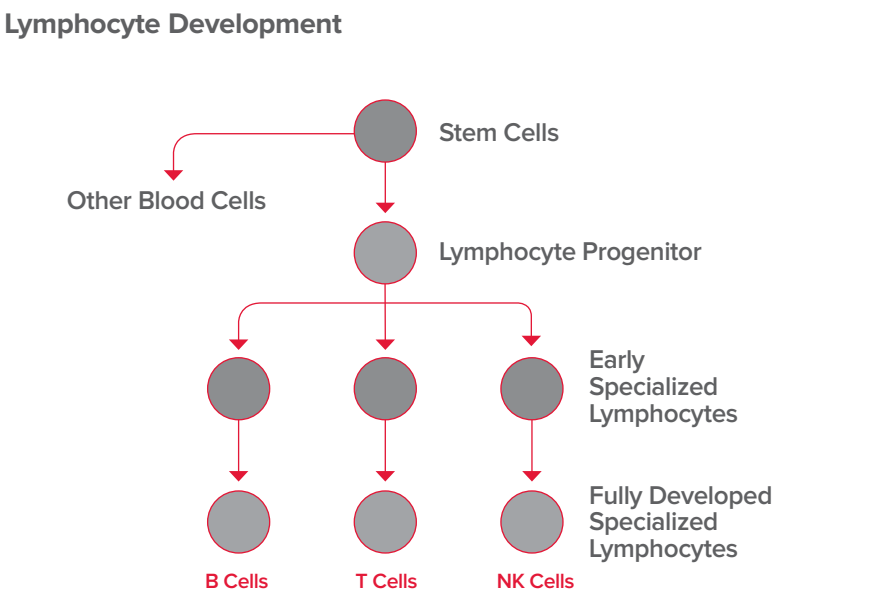

Figure 2. | Mutation of DNA can occur when the early specialized lymphocytes are formed or after the lymphocyte progenitor has differentiated into one of the three specific types of lymphocytes. The leukemic cells may be principally B cells, T cells or natural killer (NK) cells. Most patients have a B-cell type of CLL.

Immunoglobulin Levels. The measurement of the concentration of immunoglobulins (gamma globulins) in the blood is another important test. Immunoglobulins are proteins called "antibodies" that are made by B cells in healthy individuals to protect the body from infection. CLL cells do not make effective antibodies. CLL cells also interfere with the ability of the remaining normal lymphocytes to make antibodies. As a result, people with CLL often have low levels of immunoglobulins, which increases their risk of getting infections.

Treatment Planning

Treatment for CLL is always changing due to new treatments and research from clinical trials. The outlook for people with CLL is continuing to improve dramatically. New approaches to therapy have recently been FDA approved and are being studied in clinical trials for patients of all ages and at every stage of treatment. Therefore, before treatment begins, it is important to consider getting a second opinion at a center with a CLL-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.

Staging. Staging for CLL helps doctors to both assess how the disease is expected to progress over time and also to develop a treatment plan (see Table 1.). Staging systems for CLL take into account

- The elevation of blood and marrow leukemic lymphocyte counts
- The size and distribution of lymph nodes
- The spleen size
- The degree of anemia and the extent of decreased blood platelet counts.

Table 1. Commonly Used CLL Staging Systems

Rai Staging System Stage and Signs at Diagnosis	Binet Staging System Stage and Signs at Diagnosis
Low Risk—0 Abnormal increase in the number of lymphocytes in the circulating blood and marrow	**A** Abnormal increase in the number of lymphocytes in the circulating blood and less than 3 areas of palpable enlarged lymphoid tissue
Intermediate Risk—I & II Abnormal increase in the number of lymphocytes in the circulating blood and marrow and enlarged lymph nodes or Abnormal increase in the number of lymphocytes in the circulating blood and marrow and enlarged spleen and/or liver	**B** Abnormal increase in the number of lymphocytes in the circulating blood and greater than 3 areas of palpable enlarged lymphoid tissue
High Risk—III & IV Abnormal increase in the number of lymphocytes in the circulating blood and marrow and anemia (hemoglobin <11 g/dL) or Abnormal increase in the number of lymphocytes in the circulating blood and marrow and low platelet count (platelets <100,000/µL)	**C** Same as B with anemia (hemoglobin <11 g/dL in men or hemoglobin <10 g/dL in women) or low platelet count (platelets <100,000/µL)

Chromosomal Changes. Certain chromosomal changes can help the doctor to identify those people with CLL who may benefit from closer medical follow-up or certain types of therapy. About half of CLL patients who are tested with"G-banding karyotyping" are found to have CLL cells with chromosomal abnormalities. About 80 percent of CLL patients who are tested with "fluorescence in situ hybridization (FISH)" are found to have chromosomal abnormalities. The following examples are some of the more common chromosomal abnormalities:

Del(13q)	Deletions on the long arm of chromosome 13, del(13q), are the most common. Del(13q) with no other chromosomal abnormalities is associated with a relatively more favorable outcome.
Trisomy 12	About 10 to 20 percent of patients have CLL cells with three copies of chromosome 12 (trisomy 12) instead of the expected two chromosomes. Trisomy 12 is associated with intermediate-risk CLL. Trisomy 12 with other chromosomal abnormalities is associated with a higher risk than trisomy 12 alone.
Del(11q)	Up to 20 percent of people with CLL have deletions in CLL cells in the long arm of chromosome 11, del(11q). The proportion of CLL patients with del 11q tend to be younger with large lymph nodes and have high-risk disease.
Chromosome 14 or Chromosome 6	Structural abnormalities of chromosome 14 or chromosome 6 in CLL cells indicate higher-risk disease.
Del(17p)	About 5 percent of people with CLL at diagnosis have deletions in the short arm of chromosome 17, del(17p). The critical *TP53* gene in this region is typically deleted. People who have CLL with del(17p) tend to have higher-risk disease and usually do not respond as well to standard initial therapy. Their CLL treatment needs to be approached in a different manner.

Other factors may be signs of faster-growing disease (higher-risk CLL) and indicate the need for closer follow-up with the doctor. For example:

Blood lymphocyte doubling

People with CLL whose lymphocyte number doubles in one year have higher-risk CLL and need closer follow-up; a lymphocyte number that remains stable indicates a relatively lower risk.

CD38

CD is an abbreviation for "cluster designation," a term used with a number to identify a specific molecule on the surface of an immune cell. The expression of CD38 on CLL cells may be an indicator of higher-risk CLL.

B_2M

A higher level of serum beta$_2$-microglobulin (B_2M), a protein that is shed from CLL cells, is associated with a greater extent of disease. Several studies have found that B_2M and other serum markers, such as CD23, may help predict survival or progression-free survival. Tests for these markers need to be standardized, and further study in clinical trials is needed to evaluate their relative value in managing the treatments of people with CLL.

Unmutated *IgHv*

The unmutated immunoglobulin heavy chain variable region gene *(IgHv)* suggests the likelihood of higher-risk disease. Forty percent of CLL patients at diagnosis will have this whereas 60 percent will have the more favorable *IgHv*-mutated disease.

ZAP-70

ZAP-70 (zeta-associated protein 70), when increased, may be associated with higher-risk disease. It should be noted that further study in clinical trials is needed to standardize the assessment of ZAP-70. The National Comprehensive Cancer Network (NCCN) guidelines state that the evaluation of ZAP-70 expression by flow cytometry can be challenging and is not recommended outside of a clinical trial. There are new tests such as ZAP-70 methylation which may represent a better way to measure this. Additionally, other prognostic markers such as CD49d expression have also been suggested as a better biomarker than ZAP-70.

NOTCH1 gene mutations

NOTCH1 is a gene involved in the development of different type of blood cells. In CLL, approximately 10 to 15 percent of patients have mutations of this gene causing it to be more active than it should be. Several studies have suggested that CLL patients who have *NOTCH1* gene mutations may progress more quickly, requiring therapy and have a shorter overall survival. These findings are currently being confirmed. Some commercial laboratories do this test, but it is not recommended by the NCCN guidelines.

SF3B1 gene mutations

The *SF3B1* gene is involved in the forming of select proteins in CLL and other blood cancers. It is mutated in several blood cancers including CLL, AML, and MDS. In CLL, approximately 10 to 15 percent of patients have mutations of this gene, resulting in dysfunctional protein processing. Several studies have suggested that CLL patients who have *SF3B1* gene mutations may progress more quickly, requiring therapy and have a shorter remission and overall survival. These findings are currently being studied. Some commercial laboratories do this test but it is not included in the NCCN guidelines.

TP53 gene mutations

The *TP53* gene is viewed as the gatekeeper to protecting the DNA of cells from damage. Mutated DNA of cancer cells lead to increased cancer growth and resistance to chemotherapy cancer treatments. Mutation of the *TP53* gene is very commonly seen in patients who also have del(17p) findings on their interphase cytogenetics. Some patients just have mutation of the *TP53* gene and, in general, these patients have a higher likelihood of progressing more quickly, requiring therapy, not responding well to traditional therapies and having an overall shorter survival. Many commercial laboratories do this test. Select newer therapies work better for patients who have del(17p) or the *TP53* gene mutations. Given the rarity of this type of CLL, if the *TP53* gene mutation is found, it is important for you to consult a CLL specialist at a major cancer center.

Treatment

Current therapies do not offer patients a cure for CLL, but there are treatments that help manage the disease. See Table 3 on page 18. Treatments for CLL include

- Watch and wait
- Single or combination drug therapy
- Targeted therapies
- Monoclonal antibody therapies
- White blood cell (neutrophil) growth factors
- Radiation therapy (rarely used)
- Splenectomy (rarely used)
- Treatment in a clinical trial (see *Research and Clinical Trials* on page 25).
  - Drug therapy with new drugs or new drug combinations
  - High-dose chemotherapy and allogeneic stem cell transplantation.

The goals of CLL treatments are to

- Slow the growth of the CLL cells
- Provide long periods of remission (when there are no signs of CLL and/or people feel well enough to go about their day-to-day activities)
- Improve survival
- Help people to feel better when they have infections, fatigue or other symptoms.

Some people with CLL can be managed with a watch-and-wait approach for years before the disease progresses. The decision to treat a person with CLL is based on a number of factors (see Table 2).

Table 2. Some Factors That Influence the Decision to Treat Patients Who Have CLL*

Enlarging lymph nodes
Enlarging spleen
Worsening anemia
Absolute lymphocyte count (>300)**
Falling platelet count
CLL symptoms (such as fatigue, night sweats, weight loss, fever, etc.)

* Several of these factors are often present at the same time.
** Rapidly rising lymphocyte count in asymptomatic patients may not be an independent factor to begin treatment.

A person with CLL is usually treated by a hematologist/oncologist. People are advised to consult with a doctor who specializes in treating patients with leukemia and to discuss their most appropriate treatment options—including whether or not participation in a clinical trial is recommended.

Watch and Wait. People with CLL who have minimal changes in their blood counts and no symptoms are usually managed with observation alone. This approach includes

- Medical examinations
- Periodic testing to determine whether the disease is stable or beginning to progress
- Counseling by their doctors to seek medical assistance if they develop fevers or other signs of infection or illness
- Active treatment is started when, or if, the disease begins to progress.

People are often concerned when they receive a diagnosis of CLL and then learn that they will not begin treatment right away. When there are minimal changes to a person's blood counts and no symptoms, the watch-and-wait approach is the current standard of care. Many studies have compared the watch-and-wait approach to an early treatment approach for people with low-risk CLL. Study findings include the following information:

- To date, no benefits of early treatment for people with low-risk CLL have been shown.
- Several studies have confirmed that the use of alkylating agents or aggressive chemotherapy in patients with early-stage disease does not prolong survival.
- There are risks of early treatment, including potential side effects and treatment complications.
- Patients may build up a resistance to the drugs used and would not be able to use them again when treatment for progressive disease is necessary.

Deferred treatment versus early treatment for people with CLL who are symptom-free is an area of ongoing study in clinical trials.

Many patients take alternative medicines during this time period. The active ingredient of green tea, epigallocatechin gallate (EGCG), has been studied preliminarily as a therapy to prevent CLL progression and has shown very modest results but reasonable safety. Other agents have not been studied extensively in this area. Patients should discuss taking such alternative medications with their doctors. For more information about alternative therapies, see the free LLS publication *Integrative Medicine & Complementary and Alternative Therapies as a Part of Blood Cancer Care*.

Chemotherapy. Chemotherapeutic drugs target both cancer and healthy cells in the body. In most, but not all cases, chemotherapy tends to produce side effects that, in the short term, can be unpleasant. Fortunately, the drugs used for most CLL chemotherapies such as chlorambucil, cyclophosphamide, fludarabine, and bendamustine, have side effects that are mild to modest. They include lowering of the normal blood counts, increased risk of infection, nausea, vomiting, and rash.

Targeted Therapies. The drugs used in these therapies target specific substances on the cancer cell. In most cases, the drugs administered in targeted therapies are given as pills and are generally better tolerated than chemotherapy. There are two FDA approved drugs for CLL, ibrutinib (Imbruvica®) and idelalisib (Zydelig™). Additionally, drugs approved for other blood cancers, such as lenalidomide (Revlimid®), are used in CLL in some cases. The order of which of these targeted therapies to use as first, second and third treatment will be determined by future clinical trials. Participation in these trials is important to moving these non-chemotherapy based treatments forward earlier in the treatment of CLL.

Monoclonal Antibody Therapies. These types of treatments attach to the cancer cells marking them for destruction by the immune system. Examples of antibody therapies approved for CLL include rituximab (Rituxan®), ofatumumab (Arzerra®), and obinutuzumab (Gazyva®). Antibodies to other targets on CLL cells are also in clinical trials. These treatments are generally given through the vein (intravenously). The most common side effects seen with antibody therapies are signs of immune system activation (usually with the first dose) including fever, chills, shortness of breath, and sometimes low blood counts.

White Blood Cell (Neutrophil) Growth Factors. Treatment for CLL may include administering blood cell growth factors to improve low white blood cell counts. Treatment with white blood cell growth factors may help people with CLL to tolerate the side effects of higher doses of chemotherapy (see *Complications: CLL or CLL Treatment* on page 23).

Radiation Therapy. Radiation is sometimes used to shrink large lymph node masses or masses in locations that interfere with the function of a neighboring body part, such as the kidney, the gastrointestinal tract or the throat. This treatment is rarely used in CLL.

Splenectomy. CLL cells can gather in the spleen and become problematic in some people with CLL. Surgical removal (splenectomy) of a very enlarged spleen may improve blood cell counts. This approach is used selectively because it is only beneficial if the patient's spleen is affected by CLL.

Table 3. Some Approved Drugs Used to Treat Chronic Lymphocytic Leukemia

Chemotherapy

- Bendamustine (Treanda®)
- Chlorambucil (Leukeran®)
- Cladribine (Leustatin®)
- Cyclophosphamide (Cytoxan®)
- Doxorubicin (Adriamycin®)
- Fludarabine (Fludara®)
- Prednisone

Targeted Therapy

- Ibrutinib (Imbruvica®)
- Lenalidomide (Revlimid®)
- Idelalisib (Zydelig®)

Monoclonal Antibody Therapy

- Alemtuzumab (Campath®)
- Ofatumumab (Arzerra®)
- Obinutuzumab (Gazyva®)
- Rituximab (Rituxan®)

Initial Treatment of Symptomatic CLL. Treatment of CLL is started when symptoms develop that are related to the disease. These include

- Fatigue
- Enlarging lymph nodes/spleen
- Weight loss
- Night sweats
- Low red blood cell counts
- Low platelet counts.

When starting therapy, it is important to get

- Cytogenetic testing (FISH testing) done to determine if a del(17p) or del(11q) is present. If this test was not done at the time of the initial diagnosis, it should be done now. Or, this test should be repeated.

- *IgHv* gene mutational status assessed
- Testing for prior hepatitis B exposure
- A bone marrow aspirate/bone marrow biopsy
- A direct antibody test (DAT), if anemia is present, to identify possible hemolysis (red blood cell destruction).

CLL treatment is evolving and treatment options are divided by age, younger than 65 to 70 years versus older than 70 years, and the presence or absence of del(17p). In each situation, therapy with chemotherapy plus immune therapy (chemoimmunotherapy) is given. The chemotherapy and immune therapies used are summarized below for these groups.

CLL Patient Younger Than 65 to 70 Years Without del(17p): Younger patients in this category generally are treated with a chemotherapy combination that includes fludarabine and cyclophosphamide combined with an anti-CD20 antibody called "rituximab" (see *Monoclonal Antibody Therapies* on page 17). This therapy is highly effective at reducing disease and for most patients the treatment is tolerable. Studies comparing treatment with chemotherapy (fludarabine alone or fludarabine and cyclophosphamide [FC]) with chemoimmunotherapy (fludarabine and rituximab [FR] or fludarabine, cyclophosphamide and rituximab [FCR]) have shown that FR or FCR treatment significantly improved

- The frequency of complete response
- Length of remission
- Overall survival in previously untreated people with CLL (see *Treatment Response and Follow-Up Care* on page 28).

While it is clear that FCR is the best treatment for CLL patients with del(11q), the benefit of FCR (versus FR) is not as clear in other genetic groups, its benefits are currently being studied in clinical trials. Some doctors hesitate to use cyclophosphamide in FCR because there may be a higher risk of both short-and long-term complications. These complications include myelodysplasia or acute myeloid leukemia, which occurs in 3 to 10 percent of patients. However, long-term follow-up studies from younger patients in the favorable prognostic group (*IgHv*-mutated CLL) treated with FCR, show durable remissions extending beyond 10 years. In contrast, patients with *IgHv*-unmutated CLL do not attain sustainable remissions with FCR. So, it is important to identify the genetic group you belong to in order to make decisions about treatment.

Bendamustine (Treanda®) with rituximab (BR) is another chemotherapy combination that many hoped would take the place of FCR. A recent clinical trial showed BR to be inferior as initial treatment of CLL across all different genetic groups. As such, the use of this BR should generally be applied as initial therapy for CLL only when FCR is not appropriate. Examples of this might include cases when

renal insufficiency is present or autoimmune complications develop while the patient is receiving FCR.

CLL Patient Older Than 65 to 70 Years Without del(17p): Older patients represent the most common group of patients with CLL and studies have not shown much benefit to fludarabine-based treatment. This becomes more apparent as patient age increases to 70 years and beyond. Chemoimmunotherapy is still used but typically the combination chemotherapy treatment uses an oral agent called "chlorambucil" which is better tolerated than fludarabine in older patients. Typically chlorambucil is given together with a CD20 antibody, such as rituximab (Rituxan®), ofatumumab (Arzerra®), or obinutuzumab (Gazyva®), which improves response rate and remission duration. While there are no trials comparing these three antibodies directly, the only CD20 antibody that has been shown to prolong survival when combined with chlorambucil is obinutuzumab. Another chemoimmunotherapy option for this patient group is bendamustine plus rituximab although evidence that this is better than chloramubucil plus obinutuzumab is not available. Clinical trials with ibrutinib in this setting compared to standard chemotherapy (chlorambucil) and chemoimmunotherapy (bendamustine plus rituximab) are either completed or ongoing and will provide the answer of potential benefit of this targeted therapy over chemoimmunotherapy. Similarly, trials with idelalisib are beginning in this same setting in combination with other therapies. Patient participation in these trials will be critical to getting to this answer quickly.

CLL Patients With del(17p): Young and older patients with del(17p) do not respond well to any type of chemoimmunotherapy treatment. Rituximab plus high-dose methylprednisolone is a regimen that is effective for reducing CLL disease in this patient group. However, these patients are best directed toward clinical trials or novel therapies that are emerging such as ibrutinib. Compared to other treatment approaches, ibrutinib has shown high response rates, excellent remission duration and low toxicity. Based upon these promising data, the FDA recently approved ibrutinib for del(17p) patients. Early consideration of allogeneic transplant should be also considered in this patient group.

Relapsed or Refractory CLL. "Relapsed CLL" is the term for disease that responded to therapy but, after six or more months, stopped responding. "Refractory disease" is the term for CLL that does not result in a remission (but may be stable) or disease that gets worse within six months of the last treatment.

People who are treated for relapsed or refractory CLL often have good quality years of remission after more treatment. Treatment guidelines for people with relapsed CLL are generally the same as treatment for newly diagnosed people. When symptoms develop, treatments similar to those used initially can be considered. However, the results with ibrutinib thus far, which led to its recent FDA approval, suggests that it is superior to these options and better tolerated. Ibrutinib is

described below. For additional therapy options, ask your doctor about clinical trials with targeted or antibody therapies.

Information about ibrutinib (Imbruvica®).

- It is an oral targeted therapy.
- It is FDA approved for the treatment of CLL patients who have received at least one prior therapy.
- It is the best treatment for relapse regardless of different genetic groups. Patients with del(17p) or complex karyotype still have a higher risk of relapsing than other genetic groups (as with chemotherapy).
- Patients with relapsed CLL who have symptoms take ibrutinib as 3 pills (currently) once daily continuously until it does not work anymore. Patients thus far have taken ibrutinib for more than 4 years without any long-term side effects.
- Unlike chemotherapy, ibrutinib initially causes the leukemia cell count to go up as lymph nodes shrink and other components of CLL decrease. This is followed in most patients by a decline, over time, in the number of leukemia cells in the blood.
- The common early side effects of ibrutinib are rash, loose stools, heartburn, fatigue, infections and joint aches. These symptoms generally subside with time.
- Ibrutinib can increase the risk of bleeding and should not be used in conjunction with the blood thinner Coumadin®. Additionally, for minor surgeries, ibrutinib should be stopped for 3 days before and after surgery whereas for major surgeries it should be stopped for 7 days before surgery and for 7 days after surgery. These precautions decrease the risk of bleeding with ibrutinib.

Patients with del(17p) still respond to ibrutinib but they have a higher relapse rate than other patients. These people are advised to speak to their doctors about whether or not treatment in a clinical trial is a good option for them. Investigative clinical protocols for drug therapies or allogeneic stem cell transplantation may offer appropriate treatment options (see *Research and Clinical Trials* on page 25). At what point allogeneic transplant should be considered in CLL treatment (before or after ibrutinib failure) is not certain at this time.

Another very recently approved therapy for relapsed CLL is idelalisib (Zydelig™) given in combination with rituximab. Idelalisib is given as an oral pill twice daily, and the rituximab is given intravenously (IV) intermittently. Idelalisib is continued indefinitely, as long as a response continues to occur. The benefit of this therapy is seen across all different genetic groups. It is unclear what the added benefit of rituximab is to idelalisib. It is reasonable to consider

giving idelalisib by itself, especially if there is concern about prior rituximab intolerance or the difficulty of giving infusion therapy to a patient.

Information about idelalisib (Zydelig™).

- It is an oral targeted therapy.
- It is FDA approved for the treatment of relapsed CLL, given in combination with rituximab.
- It is an effective treatment for relapsed disease regardless of different genetic groups. Patients with del(17p) or complex karyotype still have a higher risk of relapsing than other genetic groups (as with chemotherapy).
- Patients with relapsed CLL who have symptoms are given idelalisib twice daily continuously until it does not work anymore or until side effects occur that require them to stop taking it.
- Unlike chemotherapy, idelalisib initially causes the leukemia blood cell count to go up as the lymph nodes and other components of CLL go down. In most patients, this is followed by a decline in the leukemia blood cells over time.
- The common side effects of idelalisib early on can be fatigue, abnormalities in liver function tests, loose stools, heartburn and infection. The liver function abnormalities can be very serious and it is important to check for this with blood tests during the first several months of therapy.
- Idelalisib can cause an immune-related colitis associated with diarrhea that often shows up at 9-12 months (or longer) on therapy. If diarrhea develops on idelalisib, it can be serious and patients should be seen by their doctor.
- Idelalisib does not cause any excess bleeding problems that are currently known. Idelalisib can be given together with blood thinners such as Coumadin®. For relapsed CLL patients that require blood thinners or have a risk factor for excess bleeding (such as hemophilia), this is probably the best initial therapy for their relapsed CLL.

Patients relapsing after receiving ibrutinib or idelalisib are relatively uncommon thus far but likely will become more frequent as additional CLL patients are treated with these drugs. Relapse can also occur as a Richter transformation (CLL transforms into lymphoma). Currently, doctors are learning how to treat these patients with other therapies and ideally such individuals should be referred to doctors who specialize in CLL where trials with new therapies are being studied. It does appear that patients who relapse after idelalisib and rituximab treatment do often respond to ibrutinib. It is not known how patients who relapse after ibrutinib will respond to idelalisib and rituximab. Patients who have signs of disease progression on either of these medications should be maintained on them until a new therapy is added. Some patients can have rapid tumor growth when these agents are stopped without the addition of a new therapy. New knowledge will likely emerge over the next 1 to 2 years about how to best treat these patients.

Complications: CLL or CLL Treatment

Infection. Infections are a common complication for people with CLL. Because of this high risk of infections, immediate vaccination for pneumococcal pneumonia with Prevnar 13® (repeated every 5 years) and a yearly flu vaccine is recommended. CLL patients do not respond well to vaccines due to their immune system depression. CLL patients should never receive live vaccines (such as the shingles vaccine).

A higher risk of infection is caused by

- The inability of the person's CLL cells to make antibodies needed to fight infections
- The effect of chemotherapy, which causes reduced cell counts for certain infection-fighting white blood cells in the blood, specifically neutrophils and monocytes.

Antibiotic therapy is usually required to treat bacterial or fungal infections during the course of the disease. People who get recurrent infections may also receive injections of immunoglobulin (gamma globulin) on a regular basis to correct the immune deficiency. This treatment is expensive, but it does decrease the frequency of infections in CLL patients with low levels of immunoglobulin in their blood.

CLL-related low blood counts are often efficiently corrected with CLL therapy. However, the use of white blood cell growth factors may benefit patients who experience prolonged low white blood cell counts after treatment. Examples of white blood cell growth factors are

- Granulocyte-colony stimulating factor (G-CSF) (filgrastim [Neupogen®] or pegfilgrastim [Neulasta®]) that can increase the number of neutrophils
- Granulocyte macrophage-colony stimulating growth factor (GM-CSF) (sargramostim [Leukine®]) that can increase the number of neutrophils and monocytes.

Anemia. Anemia (low numbers of red blood cells) is a common side effect of chemotherapy. Some people with CLL may need blood transfusions.

Richter Transformation. In about 3 to 5 percent of people with CLL, the disease transforms into an aggressive lymphoma because of a change in the characteristics of the CLL cells. This is much more common in *IgHv*-unmutated CLL. This pattern is referred to as a "Richter transformation" or "large cell transformation." People with this type of CLL may have significantly enlarged lymph nodes, and may have fevers and weight loss. Tumors of lymphocytes may also develop in parts of the body other than the lymph nodes. Richter transformation is treated with aggressive chemotherapy and reduced-intensity allogeneic transplantation, if

feasible. Outcome for patients with Richter transformation is generally poor unless it is diagnosed prior to receiving treatment for CLL. A rare variant of Richter transformation can be Hodgkin lymphoma which is treated using Hodgkin lymphoma therapy. These patients tend to do better and may be cured of this (but not the underlying CLL) with aggressive therapy.

Prolymphocytes. About 15 percent of people with CLL have leukemia cells that are a mix of lymphocytes and another type of white blood cell, called a "prolymphocyte" (see Figure 3, Panel D). Most people with this type of CLL follow a similar course to that of other people with CLL. However, for a relatively small subset of patients with this type of CLL, the blood cells may become mainly composed of prolymphocytes; the spleen may enlarge further, and the disease may become less responsive to treatment. In these cases, individuals are encouraged to talk to their doctors about the potential benefits of treatment in a clinical trial.

Lymphocytes

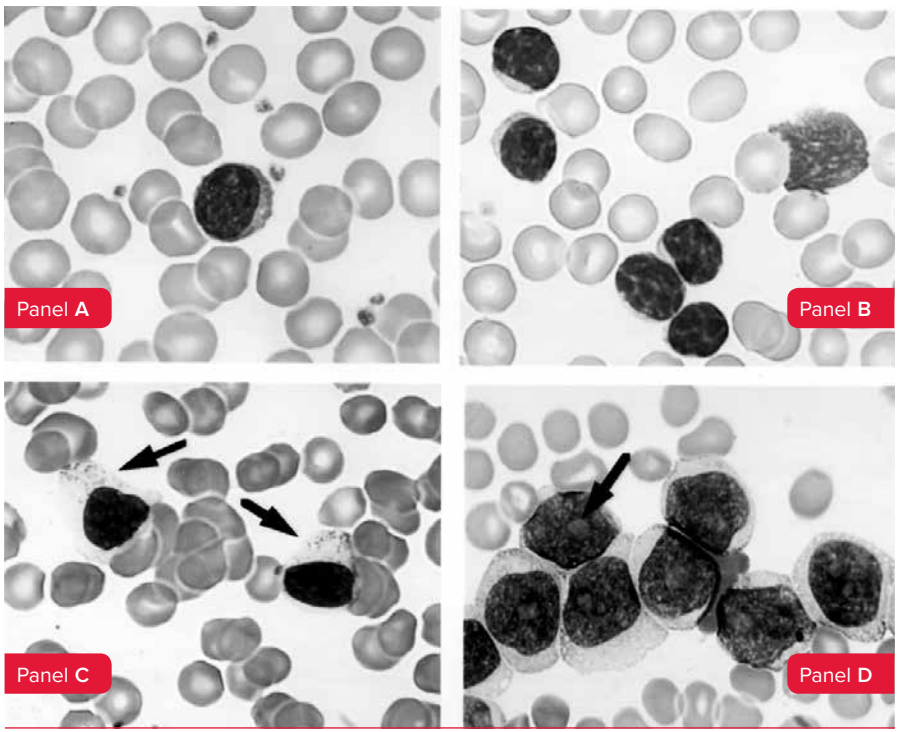

Figure 3. | **Panel A** shows a normal lymphocyte in the blood film of a healthy person. **Panel B** shows the increased frequency of lymphocytes in the blood film of a patient with CLL. **Panel C** shows the appearance of large granular lymphocytes in a patient with large granular lymphocytic leukemia (the arrows point to the cluster of granules in the cells), and **Panel D** shows the cells of prolymphocytic leukemia, which are larger than those in Panels A and B and have a light area in their nucleus, called a "nucleolus" (see arrow). This structure in the nucleus is a sign of a more immature or primitive cell.

Autoimmune Hemolytic Anemia. Some people with CLL produce a type of antibody that works against their own cells. These "autoantibodies" are usually directed against the patient's red blood cells and causes them to be removed rapidly from the blood. This condition, called "autoimmune hemolytic anemia," can worsen the effects of already low red blood cell counts. The "antiglobulin test" or "Coombs test" is used to identify the autoantibodies. Less often, the antibody works against the platelets. This condition, called "immune thrombocytopenia," results in significantly decreased platelet counts. The drugs prednisone, Rituxan® and cyclosporine are sometimes used to treat autoimmune hemolytic anemia and immune thrombocytopenia.

Second Cancers. People with CLL have a higher risk than the general population of developing a second cancer. The second cancers that are seen most frequently are melanoma, soft tissue sarcoma, colorectal cancer, lung cancer, squamous cell skin cancer and basal cell carcinoma. The recurrence rate of basal cell carcinoma after treatment is also higher for people with CLL compared to that of the general population. Both treated and untreated people with CLL can develop acute myeloid leukemia or myelodysplastic syndromes. This complication is more common after treatment with fludarabine and cyclophosphamide (FC) or fludarabine, cyclophosphamide and rituximab (FCR). Further evaluation is needed to determine whether treatment with fludarabine may increase the risk of second solid tumor cancers. It is important to follow up with your oncologist on a regular basis. More information about long-term and late effects can be found in the free LLS publication *Long-Term and Late Effects of Treatment in Adults.*

Research and Clinical Trials

CLL patients are encouraged to explore clinical trials. Clinical trials test new drugs and treatments, many of which are being supported by LLS research programs, before they are approved by the FDA as standard treatments.

Clinical trials are designed with great safety and accuracy. There are clinical trials for newly diagnosed patients and for patients who have already been treated. Sometimes, a clinical trial is the best option for a patient. Clinical trials hold great promise to increase remission rates and find a cure for CLL.

LLS Information Specialists, available at (800) 955-4572, 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 on behalf of patients, family members and healthcare professionals. This search service is also available at www.LLS.org/clinicaltrials.

Research Approaches. A number of approaches are under study in clinical trials for the treatment of patients with CLL.

New Targeted Treatments. Specific new drug therapies under study in clinical trials for people with CLL include

- **Kinase Inhibitor Therapy.** Kinases are enzymes that are found in both normal cells and cancer cells. Some cancer cells can be targeted by kinase inhibitor drugs that destroy the cancer cells. Kinase inhibitor drugs may be associated with fewer side effects than some other chemotherapy agents. There are many different kinases in CLL cells, including a phosphatidylinositol 3-kinase (PI3-kinase) and Bruton tyrosine kinase (BTK). Examples of kinase inhibitor therapy include
  - ACP-196. ACP-196 is an orally administered BTK inhibitor. This drug is in clinical trials for CLL patients. These patients have reached remission taking ACP-196 alone. The side-effect profile has been good. This drug, like ibrutinib, does cause temporary lymphocytosis (high lymphocyte count) when given by itself but this has not been shown to have any significant clinical consequence. There are other BTK inhibitors also in clinical trials at this time.
  - Duvelisib (IPI-145). Duvelisib is an orally administered PI3-kinase inhibitor. It is currently in phase 3 clinical trials for CLL where significant durable remissions have been observed. Clinical trials are now combining this with other therapeutics in CLL. This agent also causes temporary lymphocytosis (high lymphocyte count) when given by itself but this has not been shown to have any significant clinical consequence. It has many of the same side effects as idelalisib.
  - ABT-199. ABT is a B cell CLL/lymphoma 2 (BCL-2) inhibitor being studied in people with high-risk genetic features whose CLL has responded to few, if any, standard treatments. It is being studied to treat CLL or prolymphocytic leukemia that is refractory to fludarabine. It is very active in CLL and currently is being tested in phase 3 clinical trials.
  - Dinaciclib. Dinaciclib is a second-generation cyclin-dependent kinase (CDK) inhibitor being studied in patients with relapsed CLL who are not responsive to other therapies. It has shown activity in this group including patients with high-risk genetic features.

- **Monoclonal Antibody.** MOR208 is an antibody that targets CD19 on the surface of CLL cells. It is being studied in phase 1/2 clinical trials in CLL and in combination with other therapies such as lenalidomide. Antibodies and antibody-like molecules (otlertuzumab) are also being developed clinically at this time.

- **Immunomodulatory Drug.** Lenalidomide (Revlimid®) is a targeted oral drug that is used to treat patients with myeloma. It stimulates a person's own immune system to attack cancer cells. This drug is being evaluated in several CLL trials, including a phase 3 study, to determine if Revlimid, given as a maintenance therapy, is safe and effective in further improving the quality and duration of the response to treatment. This study will compare the effects of Revlimid with the effects of a placebo. Other studies include Revlimid with Rituxan® or Arzerra®; Revlimid, fludarabine and Rituxan combined for minimally treated and untreated CLL patients; and Revlimid and ibrutinib

combined for patients with advanced-relapsed or refractory CLL. One problem that has emerged in patients with long-term (maintenance) use of Revlimid in multiple myeloma has been the occurrence of secondary cancers. The relevance of this finding to CLL is uncertain although the current trials with Revlimid are being monitored very carefully for this complication. Other targeted molecules (CC-122) similar to lenalidomide are beginning clinical development in CLL.

- **Chimeric Antigen Receptor Directed T-cells (CAR-T cells)**. In this immune-directed therapy immune system T-cells are taken from your body and engineered to make them attack the CLL cells. These are then given back to the CLL patient and in early studies have generated very promising results. The early side effects of this therapy are significant and therefore it is not applied until earlier therapies described are exhausted.

Improvements in Stem Cell Transplantation. New procedures for allogeneic stem cell transplantation are being studied in clinical trials. Research teams are now trying novel ways to reduce the toxicity of transplantation and make it a possible therapy for more people with CLL.

Allogeneic stem cell transplantation is an investigational treatment option for people who have high-risk CLL that has not responded to other standard therapies. It may be an appropriate therapy for carefully selected younger people with CLL who can be matched with a stem cell donor.

A modified form of allogeneic stem cell transplantation called a "reduced-intensity" or "nonmyeloablative" allogeneic stem cell transplantation may be another transplant option for CLL patients who do not respond to other treatments. Patients being prepared for a reduced-intensity transplant receive lower dosages of chemotherapy drugs and/or radiation in preparation for the transplant, compared to the dosages given to patients receiving an allogeneic transplant.

Immunosuppressive drugs are used to prevent rejection of the donor stem cells, and the engraftment of donor immune cells may allow these cells to attack the CLL cells (called "graft-versus-tumor effect"). The theory being tested with a reduced-intensity transplant is that by undergoing less-toxic procedures prior to the stem cell transplant, the body is better able to withstand the infusion of donor cells. However, full donor engraftment would still take place, and the desired graft-versus-tumor effect would still occur. This type of transplant is generally done for high-risk CLL patients with del(17p) identified early in the course of CLL. It is also done for relapsed patients who have received multiple therapies. Even if transplant is not eventually pursued, it is important for patients with del(17p) who require therapy and patients with relapsed CLL to be referred to a transplantation expert relatively early.

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

Treatment Response and Follow-Up Care

Treatment Outcomes. Treatment outcomes for people with CLL vary widely, and expected outcomes are influenced by the stage of the disease, the presence or lack of various factors associated with higher-risk disease, the overall health of the patient and other factors. Studies suggest that newer treatment combinations and approaches may improve the length of survival. People with CLL should consult with their doctors to discuss individual potential outcomes. The National Cancer Institute-sponsored Working Group has recommended criteria to describe responses to CLL therapy. A summary of this information is presented in Table 4 on page 29; it may help people with CLL who want to discuss the results of drug studies with their doctors and to make informed treatment decisions.

Follow-Up Care. People with CLL need regular medical follow-up after they have completed treatment. It is important to assess the full effect of therapy as well as to identify any return of progressive disease that may require additional therapy.

Minimal Residual Disease. Some people with CLL have such a low level of remaining CLL cells after treatment that these cells cannot be detected by the usual clinical tests, such as blood and marrow examinations. The term used for this condition is "minimal residual disease" (MRD). More sensitive tests may be performed to detect the presence of abnormal cells. The methods generally used to detect MRD in people with CLL are four-color cell flow cytometry and polymerase chain reaction (PCR). The benefit of flow cytometry is its widespread reproducible use that now is standard as part of clinical trials. Next generation sequencing is now being tested in trials as a better method. These techniques may provide information that can help the doctor to recognize a disease relapse and to start treatment again. However, treating asymptomatic patients with MRD remains a research question and should not be pursued outside of clinical trials.

People who have been treated for CLL and/or other cancers are encouraged to keep a record of the treatments they have received. It is a good idea to share these records with the doctors who monitor general health problems, both during treatment and after treatment ends. Regular screening and monitoring for skin, colorectal, breast and other types of cancer is advised.

Table 4. Responses to CLL Therapy

Complete Response (CR)

- No evidence of clinical disease for at least two months after the completion of treatment, including normal blood count (at least 1,500 neutrophils, 100,000 platelets, and <4,000 lymphocytes per microliter (µL) of blood)
- Hemoglobin >11 g/dL without transfusions
- No CLL symptoms or enlarged lymph nodes, enlarged spleen or bone marrow involvement

Partial Response (PR)

- At least a 50 percent reduction in the number of blood lymphocytes and in lymph node and spleen enlargement
- One or more of the following must also be maintained for at least two months: platelets greater than 100,000/µL; hemoglobin >11 g/dL; or a 50 percent improvement over pretreatment red cell or platelet counts without transfusions

Nodular Partial Response

- Same as CR but with persistent lymphocytic nodules in the marrow

Progressive Disease

At least one of the following:

- Increase of at least 50 percent in absolute lymphocyte count or transformation to higher-risk disease. Lymphocytosis (high lymphocyte count) can be temporarily seen with the kinase inhibitors ibrutinib and idelalisib and do not indicate disease progression in absence of other signs
- Increase of at least 50 percent in liver or spleen size or new appearance of enlarged liver or spleen
- Increase of at least 50 percent in the sum of the products of at least two lymph nodes on two consecutive exams performed 2 weeks apart
- New appearance of enlarged lymph nodes

Stable Disease

- Absence of CR or PR, without progressive disease

Related Diseases

The diseases mentioned in this section result from the cancerous transformation of a type of lymphocyte; the accumulation of these cancer cells occurs mainly in the marrow, the blood and the spleen (see Table 5).

There are distinguishing characteristics that enable the hematologist/oncologist to identify each disease, including the appearance and the immunophenotype of the cancer cells; the cells' varying effects on normal marrow and blood cell development; and the cells' varying effects on other parts of the body, such as the kidneys, bowels and nervous system.

The diseases represent a range of clinical severity. At one end of the range, there are the diseases that may be stable and may not advance in severity for some months or years, or occasionally indefinitely. At the other end of the range, there are diseases associated with difficulties that may be present at diagnosis and possibly get worse, requiring immediate treatment and frequent observation.

Table 5. CLL and Related Diseases

Less rapidly progressive

Chronic lymphocytic leukemia
Hairy cell leukemia*
Large granular lymphocytic leukemia
Small cell lymphocytic lymphoma**
Waldenström macroglobulinemia*

More rapidly progressive

Prolymphocytic leukemia
Mantle cell lymphoma*

Most rapidly progressive

Acute lymphoblastic leukemia*

* For more information, please see the free LLS publication about this disease.
** For more information about small cell lymphocytic lymphoma, please see the free LLS publication *Non-Hodgkin Lymphoma.*

Large Granular Lymphocytic (LGL) Leukemia. LGL leukemia is type of chronic leukemia of the lymphocytes. It is characterized by larger lymphocytes containing noticeable granules, which can be seen when the blood is examined under a microscope (see Figure 3, Panel C, on page 24). These are not features of cells in other types of CLL. LGL leukemia is either T-cell type or NK-cell type. The blood lymphocyte count is always elevated in CLL. However, it is often normal or low in LGL leukemia. Although the liver and spleen may be enlarged in LGL leukemia, the lymph nodes are not. This is another feature that distinguishes it from CLL.

For patients with T-cell LGL leukemia, chemotherapy, if required, with low-dose methotrexate or cyclophosphamide, or treatment with cyclosporine, an immunomodulatory drug, may be helpful in improving the neutrophil count and the red blood cell count. Granulocyte-colony stimulating factor (G-CSF) may also be part of therapy to improve neutrophil counts, especially if an infection is present. Alemtuzumab (Campath®), which destroys large granular lymphocytes, is being studied in clinical trials as a potential treatment. Natural killer (NK) cell LGL leukemia is very resistant to therapy.

Prolymphocytic Leukemia. This disease can be a B-cell type or a T-cell type and features large numbers of lymphocytes in the blood. These lymphocytes are a mixture of small lymphocytes similar to CLL cells and large, more immature-appearing lymphocytes similar to acute lymphoblastic leukemia cells.

In general, prolymphocytic leukemia develops more rapidly than the chronic form of lymphocytic leukemia, but more slowly than the acute form. It is treated with the same drugs that are used for other types of lymphocytic leukemia. In addition, there are a number of clinical trials to study new treatment approaches for prolymphocytic leukemia.

Normal Blood and Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients throughout the body. It also carries away waste products. Blood is composed of plasma and cells.

Plasma. Plasma is largely made up of water in which many chemicals are dissolved. These chemicals each have a special role. They include

- Proteins
  - Albumin, the most common blood protein
  - Blood-clotting proteins (coagulation factors). They are made by the liver.

- Erythropoietin. It is made by the kidneys and stimulates red blood cell production.
- Immunoglobulins. These are cells that fight infection.

- Hormones, such as thyroid and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B_{12}
- Electrolytes, such as calcium, potassium and sodium.

Blood cells. The blood cells are suspended in the plasma. Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called "hematopoiesis." See Figure 4 on page 33.

Once the cell is created, it will develop into one of the three types of blood cells. These include

1. Red blood cells (the cells that carry oxygen); they

- Make up a little less than half of the body's total blood volume
- Are filled with hemoglobin, which
  - Is the protein that picks up oxygen from the lungs and takes it around the body
  - Binds with carbon dioxide (CO_2) and removes it from the cells and then brings it back to the lungs. Then the CO_2 is removed when we exhale.

2. Platelets (cells that help blood to clot); they

- Are small cells (one-tenth the size of red blood cells)
- Help stop bleeding from an injury or cut
- Stick to the torn surface of the vessel, clump together, and plug up the bleeding site. They form a clot, with the help of proteins, such as fibrin, and electrolytes, such as calcium.

3. White blood cells (WBCs) (cells that fight infections). There are several types of WBCs, including

- Neutrophils and monocytes. These are "phagocytes" (eating cells). They eat bacteria and fungi and kill them. Unlike the red cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
- Eosinophils and basophils. These WBCs respond to allergens or parasites.
- Lymphocytes. These WBCs are mostly found in the lymph nodes, spleen and lymphatic channels. They are a key part of the immune system. Some enter the

bloodstream. There are three major types of lymphocytes. They are

- T lymphocytes (T cells)
- B lymphocytes (B cells)
- Natural killer (NK) cells.

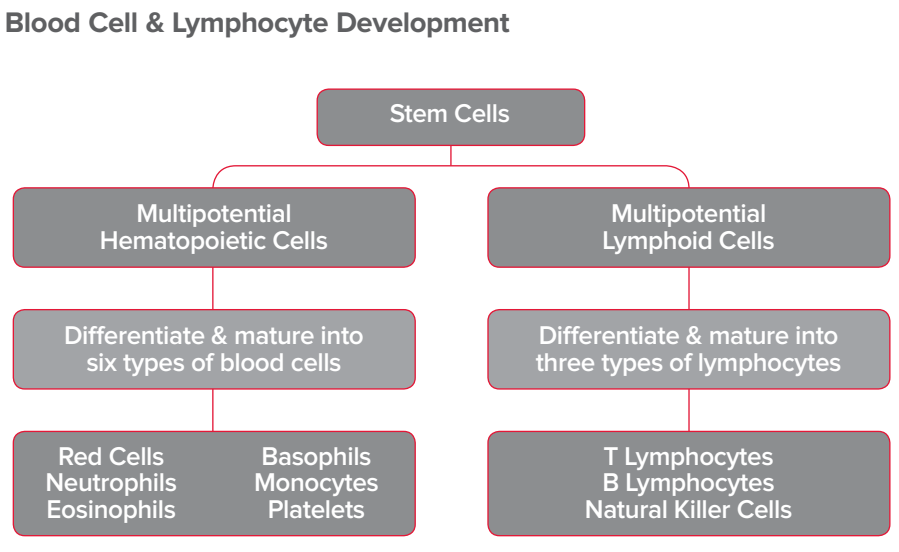

Figure 4. | **Stem cells** develop into blood cells (hematopoiesis) and lymphocytic cells.

In healthy people, stem cells in the bone marrow produce new blood cells continuously. When blood cells are fully developed, they enter the bloodstream as it passes through the marrow and then circulates throughout the body.

In babies, 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 blood-forming marrow. In adults, it is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull.

Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be transplanted. A small amount of stem cells enter the bloodstream and circulate; there are not enough of them to be counted in standard blood tests. Doctors know how to stimulate the growth of these cells in the marrow and have them migrate into the bloodstream. Then, a special technique called "apheresis" is used to separate them from the circulating blood so that they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future 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 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 (ingest it) along with its attached microbe. The white blood cell then kills and digests the microbe.
- Natural killer (NK) cells, which attack virus-infected cells or tumor cells without requiring an antibody 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.

Health Terms

Allogeneic Stem Cell Transplantation. A treatment that uses healthy donor stem cells to restore a patient's marrow and blood cells. It uses high doses of chemotherapy and sometimes radiation to "turn off" a patient's immune system so that the donor cells are not rejected. See the free LLS publication, *Blood and Marrow Stem Cell Transplantation.*

Anemia. A health condition that occurs when a person has a low number of red blood cells and therefore a low hemoglobin concentration. When this happens, it is hard for the blood to carry oxygen. People with severe anemia can be pale, weak, tired, and become short of breath.

Antibodies. A type of protein created by blood cells when they are invaded by bacteria, viruses, or other harmful things called "antigens." Antibodies help the body fight against invaders that make people get sick. Antibodies can also be made in the lab and are used to help find certain types of cancer and in treatment.

Apheresis. A process using a machine to take out needed parts of the donor's blood and return the unneeded parts to the donor. This process lets certain blood components, including red blood cells, white blood cells and platelets to be removed separately and in large volumes. See Platelet Transfusion.

Autologous Stem Cell Transplantation. A treatment that uses a patient's own stem cells to slow the growth of certain blood cancers. See the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Banding of Chromosomes. Also called "G banding," this is a technique that uses dyes to stain cells. See FISH (Fluorescence In Situ Hybridization).

Basophil. A type of white blood cell present in certain allergic reactions.

Beta$_2$-microglobulin (B_2M). A protein that is shed from CLL cells. The degree of elevation of serum B_2M appears to correlate with *IgHv*-mutation status and ZAP-70. A patient with a high level of ZAP-70 expression or an unmutated *IgHv* gene status is more likely to have a high B_2M level. This test to measure B_2M is available in most laboratories in the United States.

Blast Cells. A young (or immature) type of cell in the bone marrow. In healthy people, blast cells make up 5 percent or less of normally developing marrow cells.

Bone Marrow. A spongy tissue in the hollow central cavity of the bones where blood cells are made. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. In adults, the bones of the hands, feet, legs and arms no longer contain blood-forming marrow—these bones are filled with fat cells. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried in the bloodstream throughout the body.

Bone Marrow Aspiration. A test to find abnormal marrow cells. The area around the hip bone is numbed and then a special needle is inserted and a marrow sample (fluid) is drawn out. Usually this test is done at the same time as a bone marrow biopsy.

Bone Marrow Biopsy. A test to find abnormal marrow cells. The area around the hip bone is numbed and then a special needle is inserted and a piece of bone containing marrow is withdrawn. Usually this test is done at the same time as a bone marrow aspiration.

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

CD38. An antigen on CLL cells and other cells. The expression of CD38 may be a marker to assist in predicting CLL progression.

Central Line (Indwelling Catheter). A special tube put into a large vein in the patient's upper chest. It is used to give medications, fluids or blood products or to take blood samples. See Port.

Chemotherapy. A treatment that uses medicine (chemical agents) to kill cancer cells.

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 (XX for females and XY for males). See Translocation.

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, myeloma and myelodysplastic syndromes are examples of clonal cancers; that is, cancers derived from a single abnormal cell.

Cluster Designation (CD). A term used with a number to identify a specific molecule on the surface of an immune cell. It is commonly used in its abbreviated form, for example, "CD20" (the target of the monoclonal antibody therapy rituximab [Rituxan®] and "CD52" (the target of the monoclonal antibody therapy alemtuzumab [Campath®]).

Colony-Stimulating Factor. See Growth Factor.

Cytogenetic Analysis. A type of test that looks at the number and size of the chromosomes in cells. It is often used in cancer treatment and to see changes in the cells before and after treatment.

Cytogeneticist. A health care expert who uses special types of tests to look at cells and chromosomes.

Differentiation. When stem cells develop and mature and take on a new function. Stem cells will either mature into red blood cells, platelets or white blood cells. See Hematopoiesis.

Eosinophil. A white blood cell that helps to fight some parasitic infections and participates in allergic responses.

Erythrocytes. See Red Blood Cells.

FISH (Fluorescence In Situ Hybridization). A technique to study chromosomes in tissue. It uses probes with fluorescent molecules that emit light of different wavelengths and colors. The probes match to the chromosomes within the cells, and the chromosomes fluoresce in color. FISH can be helpful in assessing risk and treatment needs, and for monitoring treatment effectiveness, by providing a sensitive test to see abnormal cells, such as cells with deletions of 17p.

Flow Cytometry. A test that finds specific cell types within a cell sample, During this test, cells flow through the instrument called a "flow cytometer." When the cells pass through its laser beam, those with the antibody-specific features light up

and can be counted. This test may be used to examine blood cells, marrow cells, or cells from a biopsy.

G-Banding Karyotyping. A testing method that makes a certain characteristic of chromosomes easier to see. A "karyotype" is the systematic arrangement, using images, of the 46 human chromosomes of a cell. Karyotypes are examined for deviations from the expected arrangement, number, size, shape or other characteristics of the chromosomes. Each chromosome pair has a characteristic banding pattern. To make the banding pattern easier to see, a dye called "Giemsa" may be used as a stain. This process is also referred to as "G-banding." Certain chromosomal abnormalities are associated with specific CLL subtypes. G-banding karyotyping and other cytogenetic tests provide doctors with information that contributes to determining the best treatment approach for an individual patient. The test takes longer than the FISH test, but has the advantage of being able to detect any changes that are visible because it does not rely on specific probes. Usually, both tests are done on samples from the marrow, especially at the time of diagnosis.

Graft-Versus-Host Disease (GVHD). A disease that happens when a patient's white blood cells think cells from a donor's blood or marrow suspension (the graft) are enemy cells and tries to fight and destroy them. Most often this disease attacks a patient's skin, liver, and the stomach and gastrointestinal tract.

Graft-Versus-Tumor Effect (Graft-Versus-Leukemia Effect). The potential immune reaction of transplanted (donor) T lymphocytes causing them to recognize and attack the cancer cells of the patient.

Granulocyte. A type of white blood cell with many particles (granules) in the cell body. Neutrophils, eosinophils and basophils are types of granulocytes.

Growth Factor. A substance used to increase the numbers of neutrophils after chemotherapy. Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are growth factors that can be made in the lab.

Hemapheresis. See Apheresis.

Hematologist. A doctor who specializes in blood cell diseases.

Hematopathologist. A doctor or scientist who studies the blood cells and blood tissues to identify disease.

Hematopoiesis. The formation of all types of blood cells that starts in the marrow. For the blood cell development process, see *Normal Blood and Marrow* on page 31.

HLA. Human leukocyte-associated antigen. Proteins on the outer part of the cells that help fight illness. HLAs are passed from parents to their children and one in four siblings has the same type of HLA.

Immunoglobulin Heavy Chain Variable Region *(IgHv)* Gene Status. A marker that can distinguish between CLL subtypes (unmutated *IgHv* and mutated *IgHv*). People with CLL with unmutated *IgHv* gene status may have a more progressive form of the disease.

Immunophenotyping. A process used to find specific types of cells within a blood sample. It looks at antigens or markers on the surface of the cell to identify antibodies.

Indwelling Catheter. See Central Line.

Karyotype. The order, number and appearance of chromosomes within a cell. There are 46 human chromosomes with the sex chromosomes shown as a separate pair (either XX or XY). The 22 pairs with each cell are called "autosomes." See FISH (Fluorescence In Situ Hybridization).

Leukocytes. See White Blood Cells.

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

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 those sites.

Lymph Nodes. Small structures, the size of beans 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 expand the lymph nodes so that they may become enlarged.

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

Macrophage. A monocyte in action (this is called a "scavenger cell"). When monocytes leave the blood and enter the tissue, they are known as "macrophages." Macrophages fight infection, eat dead cells and help lymphocytes with their immunity functions. See Monocyte.

Minimal Residual Disease (MRD). The small amounts of cancer cells that may remain after treatment. These cells are only identified by sensitive molecular techniques.

Monoclonal. See Clonal.

Monocyte/Macrophage. A type of red blood cell that represents about 5 to 10 percent of the cells in normal human blood.

Multidrug Resistance (MDR). A cell characteristic that makes cells resistant to certain types of drugs.

Mutation. A change in the DNA that makes up a gene.

Neutropenia. An abnormal decrease in the number of neutrophils, a type of white blood cell, in the blood.

Neutrophil. A type of white blood cell and the main type that works to fight infection. People with some blood cancers, or those who have received treatment (such as chemotherapy) for cancer, often have low neutrophil counts. People with low neutrophil counts are very susceptible to infections.

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

Oncologist. A cancer doctor.

Pancytopenia. A health condition when there is a decrease in the numbers of the three major blood cell types: red blood cells, white blood cells and platelets.

Pathologist. A doctor who finds disease by examining body tissue and fluids.

Petechiae. Pinhead-sized sites of bleeding in the skin that occurs when someone has a low platelet count. They are often seen on the legs, feet, trunk and arms. Petechiae turn from red to brown, and eventually disappear. They stop developing when the platelet count increases.

Phagocytes. Cells that protect the body from infection by eating and killing microorganisms such as bacteria and fungi. Neutrophils and monocytes are the two main types of these cells. Once an infection occurs, phagocytes migrate from the bloodstream and enter the infected tissue. Chemotherapy and radiation can decrease the numbers of these cells, so patients are more likely to get an infection.

Platelets. Also known as "thrombocytes," platelets are small colorless blood cells. They travel to and collect at the site of a wound. Once they get there, the platelets' sticky surface helps them to form clots and stop bleeding. Platelets make up about one tenth of the volume of red blood cells.

Platelet Transfusion. This procedure transfers blood platelets from one patient to another. About six single-unit blood donors are often needed to provide enough platelets to raise the patient's platelet level. Platelet transfusions may help some CLL patients. For more information, see the free LLS publication *Blood Transfusion.* See HLA; Apheresis.

Polymerase Chain Reaction (PCR). A technique to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be studied.

Port. A small device placed under the skin and attached to a central line or a peripherally inserted central catheter (PICC or PIC line). It permits access to the line. Medicines and nutrition can be administered and blood samples can be withdrawn via a port.

Promyelocyte. A cell that is formed during the transition from an immature cell to a mature cell during the development cycle for certain types of red blood cells.

Red Blood Cells. Blood cells (erythrocytes) contain hemoglobin, which carries oxygen to the tissues of the body. Red blood cells make up about 40 to 45 percent of blood volume in healthy people.

Reduced-Intensity Stem Cell Transplantation. A type of allogeneic transplantation. Patients receive lower doses of chemotherapy drugs and/or radiation to prepare for a reduced-intensity transplant. This protocol may be safer than an allogeneic stem cell transplant–especially for older patients. See the free LLS publication, *Blood and Marrow Stem Cell Transplantation*.

Refractory Disease. A disease that does not go away or improve much after initial treatment.

Relapse/Recurrence. A return of the disease after it has been in remission following therapy.

Remission. When signs of a disease disappear. This usually follows treatment. The words "complete" and "partial" are sometimes used to further define 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.

Resistance to Treatment. When cancer cells continue to grow even after strong drugs and/or treatments.

Richter Transformation. In a small number of patients, there is a progression in their disease. In these patients, CLL takes on the characteristics of an aggressive lymphoma. This change is not a second cancer, but a transformation of the CLL cells.

Spleen. This organ in the left upper portion of the abdomen just under the left side of the diaphragm, acts as a blood filter. Enlargement of the spleen is called "splenomegaly." Surgical removal of the spleen is known as "splenectomy."

Stem Cells. Primitive marrow cells that mature into red blood cells, white blood cells, and blood platelets. Stem cells are mostly found in the marrow, but some leave and circulate in the bloodstream. Stem cells can be collected, preserved, and used for stem cell therapy. See Hematopoiesis.

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

Thrombocytopenia. A disorder characterized by too few platelets in the blood.

Translocation. An abnormality of chromosomes in the 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.

White Blood Cells. Also known as "leukocytes," the five types of infection-fighting cells in the blood. These include neutrophils, eosinophils, basophils, monocytes and lymphocytes.

ZAP-70. An abbreviation for the cell protein "zeta-associated protein 70." A high level of ZAP-70 expression on the cells of patients with B-cell CLL is one of several factors that may predict more progressive disease. Outside of a research laboratory this test is generally not very reliable and should not be used.

More Information

Free LLS publications include

Blood Transfusion
Cancer-Related Fatigue Facts
Choosing a Blood Cancer Specialist or Treatment Center
The CLL Guide—Information for Patients and Caregivers
Understanding Clinical Trials for Blood Cancers
Understanding Drug Therapy and Managing Side Effects
Understanding Lab and Imaging Tests

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

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Notes

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