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Chronic Lymphocytic Leukemia

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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, 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 chronic lymphocytic leukemia 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

Inside this Booklet

Acknowledgement

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Introduction

This booklet provides information about chronic lymphocytic leukemia (CLL) for patients and their families. Brief descriptions of normal blood and bone marrow, the lymphatic system and definitions of medical terms are included.

Approximately 20,110 new cases of CLL are expected to be diagnosed in 2017. As of 2013, an estimated 162,374 people are either living with or are in remission from CLL[1].

In the last few decades, doctors have learned a great deal about CLL. Advances in the treatment of this disease have resulted in improved remission rates and better outcomes for patients. The number of patients who have gone into remission is increasing. New therapies are under study in clinical trials.

[1]Source: *Facts 2016-2017*. The Leukemia and Lymphoma Society. April 2017.

Resources and Information

LLS offers free information and services to patients and families affected 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 the knowledge and skills of the members of your healthcare team.

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 am to 9 pm EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/informationspecialists
- Visit: www.LLS.org/informationspecialists.

Free Information Booklets. LLS offers free education and support booklets that can be either read online or ordered. For more information, please visit www.LLS.org/booklets.

Telephone/Web Education Programs. LLS offers free telephone/Web and video 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.

Continuing Education. LLS offers free continuing education programs for health care professionals. For more information, please visit www.LLS.org/professionalEd.

Community Resources and Networking

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. To join, visit www.LLS.org/community.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients to reach out and share information. To join, please visit www.LLS.org/chat.

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, patient care and other needs. For more information, please visit www.LLS.org/resourcedirectory.

Clinical Trials (Research Studies). New treatments for patients are underway. 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. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of 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 2-week period. For more information, please

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

Feedback. To give suggestions about this booklet, visit www.LLS.org/publicationfeedback.

Leukemia

Leukemia is a cancer of the blood and bone marrow. 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 "myeloid" (or "myelogenous") 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 (other than lymphocytes) and platelets.

Acute leukemias are rapidly progressing diseases that affect cells that are not fully developed. These cells cannot carry out their normal functions. Chronic leukemias usually progress more slowly and patients have greater numbers of mature cells. In general, these more mature cells can carry out some of their normal functions (see *Normal Blood and Bone Marrow* on page 33).

The four main types of leukemia are further classified into subtypes that are based on specific features of cells. Knowing the subtype of your disease is important because your treatment approach may be based on the subtype.

Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL). According to the World Health Organization (WHO), CLL and SLL are considered to be different manifestations of the same disease. Both diseases are the result of a change to a cell that was destined to be a lymphocyte. CLL and SLL are the progressive and uncontrolled accumulation of these abnormal (leukemic) cells in the blood, bone marrow and lymphoid tissues. The leukemic lymphocytes that are observed in people with SLL are identical to those observed in patients with CLL.

In CLL, the disease manifests as significant accumulations of the abnormal lymphocytes in the blood, marrow, spleen, and lymph nodes; whereas, in SLL the abnormal lymphocytes are primarily found in the marrow and the lymph nodes.

Talk to your doctor if you have questions about your specific diagnosis and treatment.

More information about SLL can be found in the free LLS booklet *Non-Hodgkin Lymphoma.*

Chronic Lymphocytic Leukemia

How CLL Develops. Chronic lymphocytic leukemia (CLL) results from an acquired (not present at birth) mutation (change) to the DNA (genetic material) of a single marrow cell that develops into a lymphocyte. The cells multiply, resulting in an accumulation of CLL cells in the blood, marrow, spleen, and lymph nodes. CLL cells grow and survive better than healthy cells; over time, they crowd out healthy cells.

In people with CLL, the leukemic cells do not function normally. Healthy white blood cells fight infection much more effectively. However, CLL cells do not prevent normal blood cell production as extensively as the leukemic cells do in people who have acute lymphoblastic leukemia (ALL). This important distinction is the reason why the early stage of CLL is generally less severe than that of ALL.

CLL takes different forms. Some people have a slow-growing form of the disease. People with minimal changes in their blood cell counts may have stable disease for years. Other people with CLL have faster-growing disease—the CLL cells accumulate in the marrow and blood, and there is a significant decrease in the numbers of red blood cells and platelets.

Causes and Risk Factors. There are few known risk factors for CLL.

Generally, CLL has not been linked to any environmental or external factors. However, some studies have associated exposure to Agent Orange, an herbicide used during the Vietnam War, with an increased risk of CLL. The Health and Medicine Division (formerly known as the Institute of Medicine) of the National Academy of Sciences, Engineering and Medicine issued a report "Veterans and Agent Orange: Update 2008," which concluded that there was "sufficient evidence of an association" between herbicides used in Vietnam and CLL, hairy cell leukemia and other chronic B-cell leukemias. Veterans with Agent Orange exposure may be eligible for additional VA benefits. If you fall into this group of patients, it is worth getting a formal evaluation at the US Department of Veteran Affairs. For more information, please visit www.publichealth.va.gov/exposures/agentorange/.

Genetics factors likely play a role in the development of CLL, as some families have more than one affected family member with the disease. First-degree relatives of patients with CLL are approximately 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 the most common type of leukemia in Western countries. The disease generally occurs in people who are over 50 (see Figure 1). The median age at diagnosis is 71 years.

There is also a gender predisposition because CLL affects more men than women. The reason for this is not known.

Chronic Lymphocytic Leukemia: Age-Specific Incidence Rates (2009-2013)

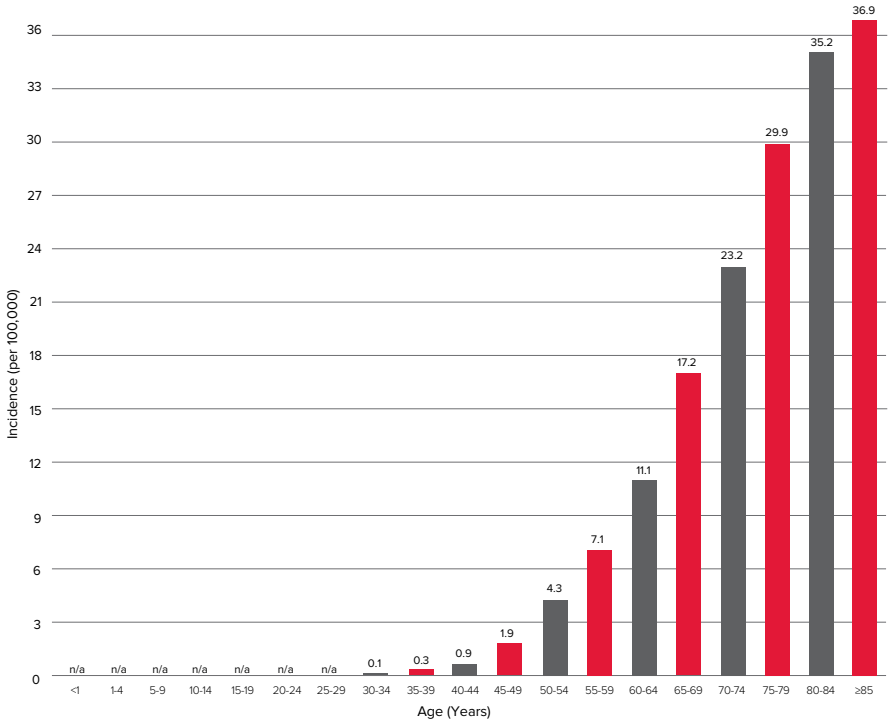

Figure 1. | The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of CLL per 100,000 people, by age-group. (source: Surveillance, Epidemiology and End Results [SEER] Program; National Cancer Institute; 2016).

Signs and Symptoms

Many people are diagnosed with CLL even though they 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.

Generally, CLL symptoms develop over time. As the disease progresses, a person may experience

- Fatigue
- Shortness of breath during normal physical activity
- Anemia (decreased red blood cell count)
- Lymph node enlargement (particularly in the neck)
- Low grade fevers
- Unexplained weight loss
- Night sweats
- Enlarged spleen or liver
- Infections of the skin, lungs, kidneys or other sites, as result of low immunoglobulin levels and decreased neutrophil counts.

Diagnosis

An accurate diagnosis of the type of leukemia is important. The exact diagnosis helps the doctor to

- Estimate how the disease will progress
- Determine the appropriate treatment.

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.

Immunophenotyping. Immunophenotyping 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 noncancerous conditions. This test is especially important if the number of lymphocytes in the blood is only slightly elevated. Immunophenotyping also determines whether the abnormal cells are from a change in either B-cell or T-cell development. If the abnormal cells are of the B-cell type, the disease is CLL. If the abnormal cells are T-cells, the disease is called "T-cell prolymphocytic leukemia" (see *CLL with Increased Prolymphocytes (CLL-PL) or Prolymphocytic Leukemia* on page 33.)

Immunophenotyping is done with an instrument called a "flow cytometer." This test can measure the number of cells in a sample and specific characteristics of the cells, including size, shape and the presence of specific markers on the cell surface. A sample of cells from blood or marrow is tagged with an antibody that is specific for a site on the cell surface. The cells, stained with a light-sensitive dye, 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. The diagnosis of CLL requires the presence of 5,000 abnormal B-cells per microliter of blood (5,000/uL).

Marrow Examination. Generally, if the red blood cells and platelets are normal, a bone marrow aspiration and biopsy are not needed to make a diagnosis of CLL. However, these tests may be recommended before treatment begins. The test results can help rule out other diseases during the diagnostic stage and they can also be used later, during treatment, to evaluate the effectiveness of therapy.

Immunoglobulin Levels. The measurement of the concentration of immunoglobulins in the blood is another important test. Immunoglobulins are proteins, called "antibodies," which 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 normal lymphocytes to make antibodies. As a result, people with CLL often have low levels of immunoglobulins, causing immune deficiency, which increases their risk of getting infections.

Treatment Planning

A diagnosis of CLL is associated with a wide range of outcomes. For the best outcome, patients are encouraged to seek treatment in a center where doctors are experienced in the diagnosis and care of patients with chronic leukemia.

Treatment for CLL is always changing due to new treatments and research from clinical trials. The outlook for people with CLL is improving. New approaches to therapy are being studied in clinical trials for patients of all ages and at every stage of treatment and several new drugs have recently been approved by the Food and Drug Administration (FDA) for treatment of patients.

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. Two staging systems, the Rai and Binet systems, are used throughout the world in both clinical practice and in clinical-trial settings. Both systems use physical examination and laboratory parameters to assess the extent of disease and to classify patients into three major prognostic groups.

Staging systems for CLL take into account

- Abnormal increase in number of lymphocytes (lymphocytosis)
- Presence of enlarged lymph nodes
- Presence of enlarged spleen and/or liver
- Presence of anemia (abnormal decrease in the number of red blood cells)
- Presence of thrombocytopenia (abnormal decrease in the number of platelets).

The original Rai staging system, created in the 1970s, proposed five different groups. This system was later revised to group patients into three separate risk groups. The Binet system is based on the number of involved areas (defined as a lymph node larger than 1 cm), the enlargement of organs (liver and spleen) and whether there are reduced numbers of red blood cells and/or platelets. (See Table 1 below and on page 11).

Commonly Used CLL Staging Systems

Rai Staging System

Stage	Characteristics
Low Risk (Stage 0)	• Abnormal increase in the number of lymphocytes in the circulating blood and marrow
Intermediate Risk (Stages I & II)	• Abnormal increase in the number of lymphocytes in the circulating blood and the marrow • Enlarged lymph nodes OR • Abnormal increase in the number of lymphocytes in the circulating blood and the marrow • Enlarged spleen and/or liver
High Risk (Stages III & IV)	• Abnormal increase in the number of lymphocytes in the circulating blood and the marrow • Anemia (hemoglobin <11g/dL) OR • Abnormal increase in the number of lymphocytes in the circulating blood and the marrow • Thrombocytopenia (platelet counts <100,000/uL)

Binet Staging System

Stage	Characteristics
A	• No anemia (hemoglobin ≥10g/dL) • No thrombocytopenia (platelets ≥100,000/mm^3) • Less than 3 areas of lymphoid tissue enlargement
B	• No anemia (hemoglobin ≥10g/dL) • No thrombocytopenia (platelets ≥100,000/mm^3) • 3 or more areas of lymphoid tissue enlargement
C	• Anemia (hemoglobin <10g/dL) • Thrombocytopenia (platelets <100,000/mm^3) • Any number of areas of lymphoid tissue enlargement

Table 1. Shows the two commonly used CLL staging systems and the characteristics of each stage.

Adapted from: National Comprehensive Cancer Network. Practice Guidelines in Oncology—v.3.2016. *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma*. Available at: www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed July 1, 2017; Hallek M. Chronic lymphocytic leukemia: 2015 update on diagnosis, risk stratification and treatment. *American Journal of Hematology.* 2015;90(5):446-460. doi:10.1002/ajh.23979.

Prognostic Factors. During the last decade, numerous markers have been identified that can help segregate patients who have different rates of disease progression requiring therapy. Some of these factors include serum markers, such as beta$_2$-microglobulin; genetic markers, including immunoglobulin heavy chain variable region (*IgHv*) gene mutational status; genetic abnormalities detected by "fluorescence in situ hybridization" (FISH) or metaphase cytogenetics; and protein markers, such as zeta-chain-associated protein kinase 70 ([ZAP]-70), cluster of differentiation CD38, or CD49d. See Table 2 on page 12 and Table 3 on pages 13 and 14 for more information on these factors.

About 80 percent of CLL patients who are tested with FISH have cytogenetic abnormalities in their leukemia cells (see Table 2 on page 12). These cytogenetic abnormalities can help the doctor identify those people with CLL who are more likely to progress to the point of requiring therapy or those who may benefit most from use of certain types of therapy.

Fluorescence in situ hybridization (FISH) is a test that studies chromosomes in tissue using DNA probes tagged with fluorescent molecules that emit light of different colors. The DNA probes then bind to specific genes or areas in the chromosomes within the cells and light up when viewed under a microscope with a special light.

Common Cytogenetic Abnormalities in CLL

Abnormality	Features	Frequency	Associated Risk
Del(13q)	Deletion (del) in the long arm of chromosome 13	55%	Favorable outcome, if not associated with any other abnormality
Trisomy 12	Three copies of chromosome 12	16%	• By itself, associated with intermediate risk CLL • If in conjunction with other abnormalities, associated with higher-risk CLL
Del(11q)	• Deletion in the long arm of chromosome 11 • Often associated with extensive lymph node involvement	18%	High risk
Del(17p)	• Deletion in short arm of chromosome 17 • Critical *TP53* gene in the region is deleted • Does not respond well to standard initial therapy	• <10% at diagnosis • up to 30% in refractory cases	High risk

Table 2. Lists some of the most common cytogenetic abnormalities in CLL, their frequency and their associated risk.

Adapted from: National Comprehensive Cancer Network. Practice Guidelines in Oncology—v.3.2016. *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma*. Available at: www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed July 1, 2017; Hallek M. Chronic lymphocytic leukemia: 2015 update on diagnosis, risk stratification and treatment. *American Journal of Hematology.* 2015;90(5):446-460. doi:10.1002/ajh.23979; Scarfò L, Ferreri AJ, Ghia P. Chronic lymphocytic leukemia (review). *Critical Reviews in Oncology/Hematology*. 2016;104:169-82. doi:10.1016/j.critrevonc.2016.06.003.

Table 3 lists other factors that may be signs of faster-growing disease (higher-risk CLL) and indicate the need for closer follow-up with the doctor.

Some Factors Associated with Higher-Risk CLL

Factor	Features and Associated Outcomes
Blood Lymphocyte Doubling	• People with CLL whose lymphocyte number doubles in 1 year have higher-risk CLL and may need closer follow-up care. • A lymphocyte number that remains stable generally indicates a relatively lower risk.
CD38	• CD is an abbreviation for "cluster designation," a term that identifies a specific molecule on the surface of an immune cell. • CD38 expression is an indicator of higher-risk CLL.
Beta$_2$-microglobulin (B_2M)	• Beta$_2$-microglobulin (B_2M) is a protein that is shed from CLL cells • It is associated with a greater extent of disease.
CD49d	• CD is an abbreviation for "cluster designation," a term that identifies a specific molecule on the surface of an immune cell. • CD49d expression is an indicator of higher-risk disease.
IgHv	• The unmutated immunoglobulin heavy chain variable region gene (*IgHv*) is associated with higher-risk disease. • About 40% of CLL patients at diagnosis have unmutated *IgHv* status while the other 60% have the more favorable *IgHv*-mutated disease. • Despite its prognostic value, assessing *IgHv* gene status is very labor intensive and not a routinely available test in many clinical laboratories.
ZAP-70	• ZAP-70 (zeta-chain-associated protein kinase 70) • Protein expressed near the surface membrane of T cells • Plays a key role in T-cell signaling • Increased expression of ZAP-70 may be associated with higher-risk disease.

***NOTCH1* Gene Mutations**	• *NOTCH1* is a gene involved in the development of different types of blood cells. • Approximately 10%–15% of CLL patients have this mutation. • CLL patients who have *NOTCH1* gene mutations may have a faster progression of disease and a less favorable outcome. • Associated with increased risk of transformation to diffuse large B-cell lymphoma (Richter transformation).
***SF3B1* Gene Mutations**	• The *SF3B1* gene is involved in the forming of select proteins in CLL and other blood cancers. • Approximately 10%–15% percent of CLL patients have this mutation, resulting in dysfunctional protein processing. • CLL patients who have *SF3B1* gene mutations may have a faster progression of disease and a less favorable outcome. • Associated with resistance to treatment with fludarabine.
***TP53* Gene Mutations**	• The *TP53* gene is considered the gatekeeper that protects cell DNA from damage. • In cancer cells this mutation leads to increased cell growth and resistance to chemotherapy. • Mutation of the *TP53* gene is very commonly seen in patients who also have deletion 17p (del[17p]). • CLL patients who have this mutation may have a faster progression of disease, resistance to traditional therapy and a less favorable outcome. • Select newer therapies (venetoclax and ibrutinib) have been approved to treat patients who have del(17p) or *TP53* gene mutations.

Table 3. Lists some factors related to higher-risk (faster-growing) CLL and their associated outcomes.

Adapted from: National Comprehensive Cancer Network. Practice Guidelines in Oncology—v.3.2016. *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma*. Available at: www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed July 1, 2017; Hallek M. Chronic lymphocytic leukemia: 2015 update on diagnosis, risk stratification and treatment. *American Journal of Hematology*. 2015;90(5):446-460. doi:10.1002/ajh.23979; Scarfò L, Ferreri AJ, Ghia P. Chronic lymphocytic leukemia. *Critical Reviews in Oncology/Hematology*. 2016;104:169-182. doi:10.1016/j.critrevonc.2016.06.003. Review; Parikh SA, Shanafelt TD. Prognostic factors and risk stratification in chronic lymphocytic leukemia. *Seminars in Oncology*. 2016; 43(2):233-240.

Treatment

During the last several decades, treatment options for CLL have evolved from the use of single and combination drug therapies. The development of targeted therapies has led to the design of new and more effective regimens, resulting in better outcomes for patients. Examples of targeted therapies are monoclonal antibodies, which target cell surface antigens, and immunomodulating agents, which work with the patient's own immune system to attack leukemic cells.

Although current therapies do not offer patients a cure for CLL, there are now many treatment options that have the potential to give patients longer remissions and a better quality of life. Treatments for CLL include

- The watch-and-wait approach
- 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 27).

The goals of CLL treatments are to

- Slow the growth of the CLL cells
- Provide long periods of remission (when there are no signs or symptoms of CLL)
- Improve survival
- Help people manage the symptoms and complications of the disease.

A person with CLL is usually treated by a hematologist/oncologist. People are advised to consult with a doctor who specializes in treating patients who have 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

- Regular medical examinations
- Regular testing to determine whether the disease is stable or beginning 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.

When to Start Treatment. 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 that indicate the progression of disease. According to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines, the following conditions define active disease:

- Enlarging lymph nodes noted over a series of clinical exams
- Enlarging liver and/or spleen noted over a series of clinical exams
- Decreased red blood cell counts (hemoglobin less than 11g/dL)
- Decreased platelet counts (platelets less than 100,000/uL)
- Autoimmune anemia and/or thrombocytopenia poorly responsive to standard therapy
- Lymphocyte doubling time of less than 6 months (only in patients with lymphocytes greater than 30g/L)
- Presence of CLL symptoms
  - Fatigue
  - Night sweats
  - Unexplained weight loss
  - Low-grade fever.

See Table 4 on page 19 for a listing of some drugs used for CLL treatment.

Drug Therapy. Chemotherapy drugs are designed to kill cancer cells. They work by attacking cells that divide quickly. Chemotherapy is typically given in cycles, with each period of treatment followed by a rest period. Corticosteroids may also be given with chemotherapy drugs.

- Antimetabolites
  - Cladribine (Leustatin®)
  - Fludarabine (Fludara®)
  - Pentostatin (Nipent®)
- Alkylating agents
  - Bendamustine hydrochloride (Bendeka®)
  - Chlorambucil (Leukeran®)
  - Cyclophosphamide (Cytoxan®)
- Corticosteroids
  - Prednisone
  - Dexamethasone.

Targeted Therapies. The drugs used in these therapies target specific parts on the cancer cell. In most cases, the drugs administered in targeted therapies are given orally and are generally better tolerated than agents used in chemotherapy.

Kinase Inhibitors. Kinases are enzymes that are found in both normal cells and cancer cells. Some cancer cells can be targeted by kinase inhibitor drugs that block survival or growth pathways in the cancer cells. Kinase inhibitor drugs may be associated with fewer side effects than chemotherapy agents. There are many different kinases in CLL cells, including phosphatidylinositol 3-kinase (PI3-kinase) and Bruton tyrosine kinase (BTK), which are the focus of several target therapy drugs.

- **Ibrutinib (Imbruvica®)** is an oral medication that blocks the activity of BTK, a kinase that helps leukemia cells grow and survive. This drug was FDA approved as a first-line treatment for patients with CLL. Ibrutinib is also approved for the treatment of hard-to-treat disease, as in the case of patients with CLL with 17p deletion (del[17p]). See page 22.
- **Idelalisib (Zydelig®)** is a targeted therapy drug that blocks the kinase protein known as "PI3K." This oral medication has been approved for the treatment of CLL that has relapsed or that is refractory to other therapies. See page 23.

BCL2 proteins and cell death. B-cell lymphoma 2 protein (BCL2) is a family of proteins that regulate cell growth and cell death. In CLL, abnormal function of BCL2 proteins prevents normal cellular death, resulting in the uncontrolled growth of cancerous cells.

- **Venetoclax (Venclexta™)** targets the BCL2 proteins, which help CLL cells avoid cell death. The Food and Drug Administration (FDA) approved this oral medication for the treatment of patients with chronic lymphocytic leukemia with 17p deletion (as detected by an FDA-approved test) who have received at least one prior form of therapy.

Monoclonal Antibody Therapies. Monoclonal antibodies are proteins made in the laboratory that either react with or attach to specific antigens on the target cells. Examples of antibody therapies approved for CLL include

Monoclonal antibodies that target CD52

- **Alemtuzumab (Campath®)**—Targets the CD52 antigen found on the surface of CLL cells. It is used to treat patients with CLL who are not responding to standard chemotherapy treatments but it can also be used earlier in the course of the disease.

Monoclonal antibodies that target CD20

- **Rituximab (Rituxan®)**—Rituximab has become one of the standard treatments for CLL. It is typically used along with chemotherapy, either as part of initial treatment or as part of a second-line regimen but it may be also used as a monotherapy agent.
- **Rituximab and hyaluronidase human (Rituxan Hycela™)**—Given subcutaneously, this drug is FDA approved for patients with previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide (FC). Treatment with Rituxan Hycela should only be used after patients have received at least one full dose of a rituximab product intravenously.
- **Ofatumumab (Arzerra®)**—Generally, ofatumumab is used if CLL does not respond to other treatments, such as chemotherapy, or other monoclonal antibodies. Ofatumumab is FDA approved in combination with chlorambucil for previously untreated patients for whom fludarabine-based therapy is considered inappropriate; in combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL; for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL; and for the treatment of patients with CLL refractory to fludarabine and alemtuzumab.
- **Obinutuzumab (Gazyva®)**—It is used in combination with the chemotherapeutic agent chlorambucil as part of initial treatment for CLL.

Radiation Therapy. Radiation therapy uses high-energy rays to destroy cancer cells. It is typically not part of standard CLL treatment but it is sometimes used to shrink an enlarged spleen, 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. It can also be helpful in treating pain from bone damage caused by leukemia growing in the marrow. This type of therapy is rarely used in CLL.

Some Drugs Used for Treatment and/or in Clinical Trials for CLL

Most antileukemic drugs interact with the cell's genetic material (DNA).

Alkylating agents

- Bendamustine hydrochloride (Bendeka®)
- Chlorambucil (Leukeran®)

Antitumor Antibiotic

- Doxorubicin (Adriamycin®)

DNA-Damaging Agent

- Cyclophosphamide (Cytoxan®)

Tyrosine Kinase Inhibitor

- Dasatinib (Sprycel®)

Antimetabolites

- Cladribine (2-CdA; Leustatin®)
- Fudarabine (Fludara®)
- Pentostatin (Nipent®)

Corticosteroids

- Prednisone
- Dexamethasone

Targeted Therapies

- Ibrutinib (Imbruvica®)
- Lenalidomide (Revlimid®)
- Idelalisib (Zydelig®)
- Venetoclax (Venclexta™)

Monoclonal Antibodies

- Alemtuzumab (Campath®)
- Obinutuzumab (Gazyva®)
- Ofatumumab (Arzerra®)
- Rituximab (Rituxan®)
- Rituximab and hyaluronidase human (Rituxan Hycela™)

Table 4. Lists some of the standard treatment drugs and some of the drugs being studied to treat CLL patients. Various approaches to CLL treatment are undergoing study in clinical trials. A patient may be treated with drugs that are not listed in this table and still be receiving appropriate and effective treatment.

Adapted from: National Comprehensive Cancer Network. Practice Guidelines in Oncology—v.3.2016; *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.* Available at: www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed July 1, 2017; PDQ® Adult Treatment Editorial Board. PDQ® Chronic Lymphocytic Leukemia Treatment—Health professional version. Bethesda, MD: National Cancer Institute. Updated 07/05/2016. Available at: https://www.cancer.gov/types/leukemia/hp/cll-treatment -pdq. Accessed 07/05/2016. [PMID:26389470]; Hallek M. Chronic lymphocytic leukemia: 2015 update on diagnosis, risk stratification and treatment. *American Journal of Hematology.* 2015;90(5):446-460. doi:10.1002/ajh.23979.

Splenectomy. CLL cells can gather in the spleen in some people with CLL. Sometimes the spleen becomes so enlarged that it starts pressing on nearby organs causing discomfort. Surgical removal (splenectomy) of a very enlarged spleen may improve blood cell counts and reduce the need for transfusions. This approach is used selectively for patients who have severe recurrent bouts of autoimmune diseases that target either the red blood cells (e.g., autoimmune hemolytic anemia [AIHA]) or platelets (e.g., immune thrombocytopenic purpura [ITP]). In such cases, removal of the spleen can help reduce the severity of the anemia (in AIHA) or a low platelet count (in ITP).

Initial Treatment of Symptomatic CLL. Treatment of CLL is started when symptoms develop that are associated with active disease.

Before 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. If previous testing was done months or years ago, this test should be repeated.
- *IgHv* gene mutational status assessed
- Testing for prior hepatitis B exposure
- A bone marrow aspiration and biopsy
- A direct antibody test (DAT, also known as the "direct Coombs test"), if anemia is present, to identify possible hemolysis (red blood cell destruction).

Because CLL is a disease of elderly patients (median age at diagnosis is 71 years), the evaluation of a patient's fitness and the identification of other medical conditions or problems (comorbidities) that may affect CLL treatment is very important. CLL treatment options are determined by the patient's age: the treatment for those younger than 65 to 70 years (fit patients) versus the treatment for those older than 70 years (less fit patients).

Another important factor for the choice of treatment is the patient's genetic CLL risk profile. For instance, the deletion of the short arm of chromosome 17 (del[17p]) is associated with a less favorable prognosis and resistance to chemotherapy. Thus, the presence or absence of del(17p) is essential information that must be taken into account when determining the choice of treatment.

CLL Patients Younger Than 65 to 70 Years Without del(17p)—the Fit Category. Younger patients in the fit category typically have no significant comorbidities and are eligible for intensive chemoimmunotherapy. These patients are generally treated with a chemotherapy combination that includes fludarabine and cyclophosphamide, combined with the anti-CD20 antibody rituximab (see

Monoclonal Antibody Therapies on page 18). This therapy is highly effective at reducing disease and, for most patients, the treatment is tolerable as it has very few side effects.

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.

Thus, treatment with FCR has become the standard of care for this group of patients. Results from longer follow-up studies have shown that a significant number of patients that received this therapy remain without detectable disease 10 years after the end of treatment. However, there are some complications associated with this therapy. Some studies have indicated a higher incidence of neutropenia and a more frequent occurrence of viral and bacterial infections for up to 2 years after the completion of treatment. Based on these data, FCR is the standard first-line treatment for patients who are 65 years or younger.

Another option, bendamustine hydrochloride (Bendeka®), an alkylating agent given intravenously, has been FDA approved for the treatment of patients with CLL.

CLL Patient Older Than 65 to 70 Years Without del(17p). For some older patients, the combination of bendamustine with rituximab (BR) may be a good option. Examples of this might include cases when renal insufficiency is present or autoimmune complications develop while the patient is receiving FCR.

Older adults (those older than 70 years) or patients with significant comorbidities are considered to be in the less fit category. Studies have not shown that fludarabine-based treatment especially benefits these older patients, the largest number of patients with CLL. This treatment becomes even less effective as patient age increases to 70 years and older.

Chemoimmunotherapy is still used. Typically, combination chemotherapy treatment uses an oral agent called "chlorambucil," which is better tolerated than fludarabine in older patients. Chlorambucil is given together with a CD20 antibody, such as rituximab (Rituxan®), ofatumumab (Arzerra®), or obinutuzumab (Gazyva®); these drug combinations improve response rate and remission duration. Among these three options, the combinations that have shown the best results in prolonging survival are obinutuzumab and chlorambucil and ofatumumab and chlorambucil. Based on these results, both combinations have been approved for first-line treatment of CLL patients.

CLL Patients with del(17p) or *TP53* gene mutations—the high-risk category. Young patients and older patients with del(17p) or *TP53* mutations do not respond well to any type of chemoimmunotherapy treatment or are likely to have early relapses after first-line therapy. 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, such as ibrutinib (Imbruvica®) and venetoclax (Venclexta™). 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 6 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 6 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 guidelines for newly diagnosed people. When symptoms develop, treatments similar to those used initially can be considered.

Drug therapy that can be used to treat relapsed or refractory CLL includes

- Alemtuzumab (Campath®)
- Ibrutinib (Imbruvica®)
- Idelalisib (Zydelig®)
- Ofatumumab (Arzerra®)
- Rituximab (Rituxan®)
- Venetoclax (Venclexta™)

See page 17 for more information about these treatments.

Ibrutinib (Imbruvica®) is approved for treatment of relapsed CLL patients. Idelalisib (Zydelig®), given in combination with the monoclonal antibody rituximab, is another therapy for patients with relapsed CLL. This drug, in combination with rituximab, is approved for the treatment for patients with relapsed or refractory CLL who have received at least one prior form of treatment. Idelalisib is given as an oral pill twice daily, and rituximab is given intravenously (IV) intermittently. Idelalisib is continued indefinitely, as long as there is a good treatment response.

Information about ibrutinib (Imbruvica®)

- It is an oral targeted therapy.
- It is FDA approved for the treatment of CLL patients and CLL patients with 17p deletion.
- It is the best treatment for relapse, regardless of different genetic groups. Patients with del(17p) or a complex karyotype still have a higher risk of relapsing than patients in other genetic groups.
- Symptomatic patients with relapsed CLL take ibrutinib as three capsules 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. 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) do respond to ibrutinib but they may have a higher relapse rate than other patients. These people are advised to speak to their doctors about whether treatment in a clinical trial is a good option for them. Clinical trials involving drug therapies or allogeneic stem cell transplantation may offer more appropriate treatment options (see *Research and Clinical Trials* on page 27).

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 a complex karyotype still have a higher risk of relapsing than patients in other genetic groups.
- 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 number of leukemia blood cells over time.

- The common side effects of idelalisib early on can be fatigue, abnormalities in liver function test results, loose stools, heartburn and infection. The liver function abnormalities can be very serious and it is important to monitor liver function with blood tests during the first several months of therapy.
- Idelalisib can cause an immune-related colitis associated with diarrhea that often shows up after 9 to 12 months (or longer) on therapy. Patients should be seen by their doctor if diarrhea develops.
- Idelalisib is not known to cause any excess bleeding problems. It can be given together with blood thinners, such as Coumadin®. This is probably the best initial therapy for patients with relapsed CLL who require blood thinners or have a risk factor for excess bleeding (eg, hemophilia).

Doctors deciding whether to treat with ibrutinib and idelalisib will keep in mind the side effects of both medications and tailor the treatment to the individual patient situation.

Patients who have signs of disease progression while they are taking 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.

Stem Cell Transplantation. Allogeneic stem cell transplantation is a treatment option for people who have relapsed or refractory high-risk CLL. 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. This type of transplant is generally done for high-risk CLL patients who have del(17p) or *TP53* gene mutations, 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 high-risk CLL who require therapy and patients with relapsed CLL to be evaluated for potential transplantation relatively early in the course of the disease.

Complications of CLL or CLL Treatment

Infection. CLL patients may be more susceptible to infections due to either the CLL itself and/or to its treatment. 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 blood cell counts for certain infection-fighting white blood cells in the blood, specifically neutrophils and monocytes.

Because of the increased risk for infection, vaccination for pneumococcal pneumonia (repeated every 5 years) and a yearly flu vaccine is recommended. CLL patients should never receive live vaccines (such as the shingles vaccine).

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.

CMV (cytomegalovirus) reactivation can occur in about 10 to 25 percent of patients with relapsed or refractory CLL treated with alemtuzumab. It is important to monitor for this potential problems during alemtuzumab therapy. Appropriate anti-infection prophylaxis and routine monitoring for early signs of infection should be considered when patients receive therapy with this particular drug.

Low Blood Cell Counts. Supportive care for CLL may include administering blood cell growth factors to improve low blood cell counts. 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.

Richter Transformation. In about 2 to 10 percent of people with CLL, the disease transforms into diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma during the course of their disease and treatment. This is known as "Richter transformation" or "Richter's syndrome." This syndrome is much more common in patients with *IgHv*-unmutated CLL. Patients may have significantly enlarged lymph nodes, and may experience fevers and weight loss. Lymphocyte masses may also develop in parts of the body other than the lymph nodes.

Patients with Richter transformation should be treated with chemoimmunotherapy regimens designed for DLBCL. Allogeneic stem cell transplantation can also be considered following a response to initial therapy. Outcome for patients with Richter transformation is generally poor unless it is diagnosed before they received treatment for CLL.

Standard Hodgkin lymphoma therapy is used for patients with Richter transformation whose CLL has transformed to Hodgkin lymphoma. With aggressive therapy, these patients tend to do better and may be cured of this condition (although not the underlying CLL).

Autoimmune Cytopenias. Autoimmune hemolytic anemia (AIHA), immunemediated thrombocytopenia (also known as "immune thrombocytopenic purpura" [ITP]) and pure red blood cell aplasia (PRCA) are the most frequent autoimmune cytopenias in CLL patients. Bone marrow tests are used to confirm the presence of these conditions.

AIHA is the most common form of autoimmune cytopenia. Patients who have AIHA produce antibodies that work 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. The loss of these red blood cells can worsen the effects of already low red blood cell counts. The direct antiglobulin test (DAT, also known as the "direct Coombs test") is used to identify the autoantibodies; however, most patients with AIHA have a negative DAT test result. In these cases, additional serum markers, such as low haptoglobin (a blood protein) and elevated reticulocyte (immature red blood cell) levels are required to make the diagnosis. Patients with advanced disease; high-risk factors, such as unmutated gene status; increased serum beta$_2$-microglobulin levels; and high expression of ZAP-70 are also more likely to develop AIHA. Less often, the antibody works against the platelets. This condition, called "immune thrombocytopenic purpura" (ITP), results in significantly decreased platelet counts.

The drugs prednisone, rituximab and cyclosporine are sometimes used to treat AIHA and ITP. Splenectomy should be considered in cases where the patient does not respond to steroid therapy. The drugs romiplostim (Nplate®) and eltrombopag (Promacta®) are both FDA approved for the treatment of thrombocytopenia in patients with ITP that is resistant to other treatments.

Tumor Flare Reactions. Tumor flare is a painful enlargement of the lymph nodes that may be accompanied by elevated lymphocyte counts, enlarged spleen, low-grade fever, rash and bone pain. These reactions are commonly seen in CLL patients treated with lenalidomide. Use of steroid medications to control the inflammation and antihistamines to manage the rash are recommended.

Second Cancers. People with CLL have a higher risk than people in the general population of developing a second cancer. This may be due to abnormalities in immune function associated with the disease and to the use of chemotherapeutic agents, which can induce potentially long-lasting remissions but are also associated with prolonged immunosuppression.

The second cancers that are seen most frequently in CLL patients are acute myeloid leukemia, myelodysplastic syndromes, melanoma, gastrointestinal cancer, breast

cancer, lung cancer, nonmelanoma skin cancer, prostate cancer, kidney cancer, bladder cancer and head and neck cancers.

Both treated and untreated people with CLL can develop acute myeloid leukemia or myelodysplastic syndromes. These complications are more common after treatment with fludarabine and cyclophosphamide (FC) or fludarabine, cyclophosphamide and rituximab (FCR).

Although all CLL patients should be counseled about their increased risk for developing a second cancer, studies indicate there are some factors that may help predict the development of other malignancies in CLL patients. These include

- Older age (older than 60 years)
- Male gender
- Elevated levels of certain blood markers, such as beta$_2$-microglobulin, lactate dehydrogenase and serum creatinine.

It is important to follow up with your oncologist on a regular basis because of the increased risk of second cancers associated with CLL.

More information about long-term and late effects can be found in the free LLS booklet *Long-Term and Late Effects of Treatment in Adults Facts*.

Research and Clinical Trials

New approaches under study in clinical trials for CLL treatment, many of which are being supported by LLS research programs, hold the promise of increasing the rate of remission and finding a cure for CLL.

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 healthcare professional to determine if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct individualized clinical-trial searches for patients, family members and healthcare professionals. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

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.** Some types of cancer can be treated by kinase inhibitor drugs that target specific enzymes in the cancer cells, which are involved in cell growth and death. These drugs may be associated with fewer side effects than traditional chemotherapy agents. An example of a kinase inhibitor therapy drug under study in clinical trials includes acalabrutinib (ACP-196). Acalabrutinib is a second-generation Bruton tyrosine kinase (BTK) inhibitor that is administered orally. This drug is being studied in clinical trials for relapsed/refractory CLL patients, including those with del(17p).
- **Monoclonal Antibodies.**
  - **Veltuzumab (IMMU-106).** This anti-CD20 monoclonal antibody has shown promising results in CLL treatment for previously untreated patients and patients whose disease has relapsed.
  - **Lucatumumab.** This is an anti-CD40 antibody currently being studied in patients with CLL that has relapsed or is refractory to therapy with fludarabine.
  - **Cirmtuzumab.** This is a humanized monoclonal antibody that binds to ROR1, a protein found on the surface of CLL cells.
- **Combinations of Antibodies With Other Targeted Drugs (Being Investigated in Clinical Trials)**
  - **Combinations with BTK and phosphatidylinositol kinase (PIK) inhibitors.** The combination of ibrutinib and rituximab is being studied in the treatment of patients who have high-risk CLL with del(17p).
  - **Combinations with immunomodulatory drugs.** A study of lenalidomide, rituximab and ibrutinib is researching the effectiveness of this combination for patients with relapsed and refractory CLL.
  - **Combinations with BCL2 inhibitors.** Venetoclax (Venclexta™) is a BCL2 inhibitor approved for treatment of CLL patients with 17p deletion. It is being studied, in combination with rituximab, for treating patients with relapsed or refractory CLL and for older, untreated patients with CLL and SLL.
- **Immunotoxin.** An immunotoxin known as "BL22" has shown promising results in treating hairy cell leukemia. A newer version of this drug HA22 (CAT-8015) is now being studied as therapy for relapsed or refractory CLL.
- **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 to determine if it can be used as a maintenance therapy and whether it is safe

and effective in further improving the quality and duration of the response to treatment. Clinical trials are also researching the use of lenalidomide in various combinations with other agents, such as rituximab, for first-line CLL treatment and in combination with the BTK inhibitor ibrutinib for patients with advanced relapsed or refractory CLL.

- **CAR T-Cell Therapy.** This is a type of immunotherapy that consists of engineering patients' own immune cells first to recognize and then to attack cancerous tumors. This approach has shown very promising results in patients with blood cancers. The T cells are genetically engineered to produce receptors on their surface called "chimeric antigen receptors (CARs)." These receptors recognize and bind to a specific target found on the cancerous cells. Current clinical trials are studying the use of CAR T-cell therapy, directed to CD19, in the treatment of chemotherapy-resistant or relapsed CLL. The results of recent trials have demonstrated that this new approach can induce long-term, disease-free remissions in CLL patients.

  For more information on this type of therapy, please see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts*.

- **PD-1 Checkpoint Inhibitors.** A vital part of the immune system is its ability to distinguish healthy cells in the body from those that it recognizes as foreign or harmful. The immune system depends on multiple checkpoints—molecules on certain immune cells that need to be activated (or turned off) in order to start an immune response. Cancer cells sometimes take advantage of these checkpoints to escape the detection of active immune cells. Programmed cell death 1 (PD-1) is a checkpoint protein that is found on the surface of T cells. It normally acts as a type of "off switch" that helps keep immune cells from attacking healthy cells in the body. It accomplishes this when it attaches to a PD-L1—a protein found on some normal cells and also in some cancer cells. When PD-1 binds to PD-L1, a message is sent to the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1 receptors, which help them avoid an immune attack. Checkpoint inhibitors are drugs created to target the PD-1 or PD-L1, blocking their actions, and allowing the immune system to recognize and eliminate cancer cells. Nivolumab (Opdivo®) is one example of this type of drug. This medication has shown great results in other cancers, such as melanoma. Now it is being studied, in combination with the drug ibrutinib, for the treatment of patients who have relapsed or refractory CLL and for patients who have high-risk CLL but have not received any prior treatment.

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 considerations. Current research suggests 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.

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 bone marrow examinations. This is called "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 multicolor cell flow cytometry and polymerase chain reaction (PCR).

Having a negative MRD status after the end of treatment is emerging as an important factor that can predict the effectiveness of the treatment received. In addition, assessing MRD status can provide information to help the doctor recognize a disease relapse and decide if the continuation of treatment is necessary. Another proposed goal of MRD assessment is to eventually develop risk-adapted treatment strategies for CLL patients. Patients who have MRD after the end of treatment could be candidates for treatment intensification, consolidation and maintenance strategies. Those who achieve early MRD-negative status may be candidates for treatment de-escalation. However, to achieve this long-term goal, highly sensitive and specific MRD detection methodology must be available and further study on the predictive capacity of these methods will be necessary.

See Table 5 on page 31 for a description of various types of CLL treatment responses.

Responses to CLL Treatment

Criteria	CR (Complete Response)	PR (Partial Response)	PD (Progressive Disease)
Lymph Node Involvement	None >1.5 cm	Decrease ≥50%	Increase ≥50%
Liver Enlargement	None	Decrease ≥50%	Increase ≥50%
Spleen Enlargement	None	Decrease ≥50%	Increase ≥50%
Bone Marrow	<30% lymphocytes No B-lymphoid nodules	50% reduction of abnormal cells in marrow or B-lymphoid nodules	
Blood Lymphocytes	<4,000/uL	Decrease ≥50% over baseline	Increase ≥50% over baseline
Platelet Count (without growth factors)	>100,000/uL	>100,000/uL or increase ≥50% over baseline	Decrease ≥50% over baseline secondary to CLL
Hemoglobin (without transfusions or growth factors)	>11.0 g/dL	>11 g/dL or increase ≥50% over baseline	Decrease of >2g/dL from baseline secondary to CLL
Neutrophil Count (without growth factors)	>1500/uL	>1500/uL or >50% improvement over baseline	

Table 5. Lists and defines the criteria for different responses to CLL treatment.

Adapted from: Comprehensive Cancer Network. Practice Guidelines in Oncology—v.3.2016. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Available at: www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed July 1, 2017; Scarfò L, Ferreri AJ, Ghia P. Chronic lymphocytic leukaemia (review). *Critical Reviews in Oncology/Hematology*. 2016;104:169-82. doi:10.1016/j.critrevonc.2016.06.003.

Follow-Up Care. After treatment, a patient who is in remission and has completed therapy continues to be examined regularly by his or her doctors. Careful periodic assessment of the patient's health, blood cell counts and, if indicated, other testing may be required to assess the full effect of therapy as well as to identify disease relapse. As time progresses, assessments may become less frequent, but should continue for as long as indicated by the healthcare professional.

People who have been treated for CLL are encouraged to

- Keep a record of the treatments they have received. This information can help the doctor to follow up on specific late effects that may be associated with those treatments, as well as develop a follow-up schedule.

  Records should include the patient's diagnosis, the names of chemotherapy drugs taken, any information about any radiation, surgery or transplantation

therapy received, information about any other treatments, and the names and dates of any significant complications and the treatment received for those complications.

- Receive periodic screening and monitoring for skin, gastrointestinal, kidney, bladder, prostate, breast, lung, head and neck and other types of cancer because of the increased risk of second cancers associated with CLL (see *Second Cancers* on page 26)
- Consider cancer risk-reduction strategies, such as smoking cessation, skin protection against prolonged sun exposure, healthy eating and exercising.

For additional information, including risks of specific chemotherapy agents, see the free LLS booklet *Long-Term and Late Effects of Treatment in Adults Facts*.

Related Diseases

Diseases related to CLL, such as prolymphocytic leukemia, result from the cancerous transformation of a type of lymphocyte; the accumulation of these cancer cells occurs mainly in the bone marrow, the blood and the spleen.

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 related diseases listed on Table 6 (on page 33) 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 complications that may be present at diagnosis and that can possibly get worse without rapid intervention, requiring immediate treatment and frequent observation.

Related Diseases

Less rapidly progressive

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 booklet about this disease.
** For more information about small cell lymphocytic lymphoma, please see the free LLS booklet *Non-Hodgkin Lymphoma.*
*** For more information, please visit the webpage www.LLS.org/LGL.

Table 6. Lists several diseases related to CLL.

CLL with Increased Prolymphocytes (CLL-PL) or Prolymphocytic Leukemia. 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." Most people with this type of CLL follow a similar disease course to that of typical CLL. However, for a relatively small group 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 more aggressive and less responsive to treatment. In these cases, patients are encouraged to talk to their doctors about participating in a clinical trial.

Normal Blood and Bone 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. This is 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 2 on page 35.

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

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. It binds with carbon dioxide (CO_2) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO_2 is removed from the lungs.
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.

Blood Cell & Lymphocyte Development

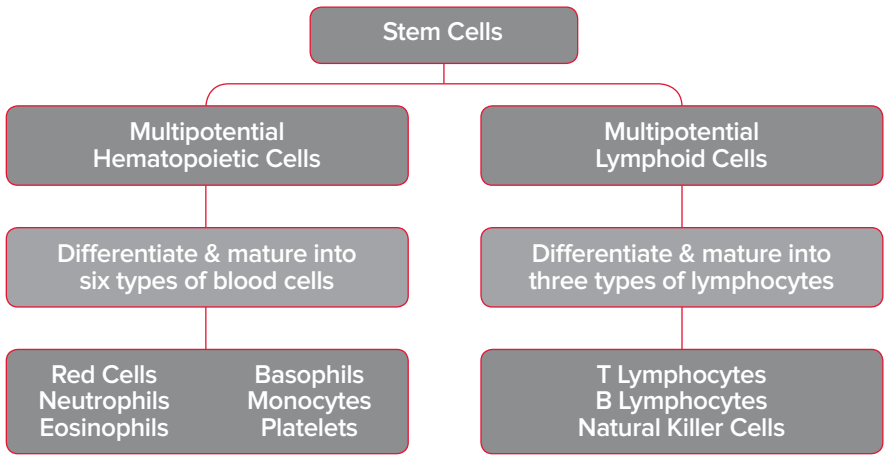

Figure 2. | **Stem cells** develop into blood cells (hematopoiesis) and lymphocytic cells.

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.

Medical 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 booklet, *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.

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 levels 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.

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.

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

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 identify cells from a donor's blood or marrow suspension (the graft) as enemy cells and try 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.

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 Bone Marrow* on page 33.

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.

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); G-Banding Karyotyping.

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 lymphocytes 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/Macrophage.

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.

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.

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

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 booklet *Blood Transfusion*. See 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.

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 booklet, *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 administration of 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.

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. They are neutrophils, eosinophils, basophils, monocytes and lymphocytes.

ZAP-70. An abbreviation for the cell protein "zeta-chain-associated protein kinase 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 booklets include

Blood and Marrow Stem Cell Transplantation
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/suggestedreading to see helpful books on a wide range of topics.

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