

Chronic Lymphocytic Leukemia (CLL)



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Introduction

Chronic lymphocytic leukemia (CLL) is a type of cancer of the lymphocytes (a kind of white blood cell). The variant of this disease in which there are not a lot of abnormal lymphocytes in the blood is also called small lymphocytic lymphoma (SLL). CLL is one of the most common blood cancers in the United States.

The course of CLL varies a lot. Most patients do not need treatment at diagnosis, but they need to be monitored carefully for progression of their disease. A small number of patients have advanced disease at diagnosis and require treatment right away, but most will not need treatment until a later time. A few patients will never need specific treatment of their CLL.

Testing the characteristics of the abnormal blood lymphocytes can be very helpful in predicting the behavior of a patient's CLL. However, some testing is still only available on a limited basis. Wilmot Cancer Center offers this testing of the lymphocytes.

Standard treatment for CLL is usually very effective, but it is not curative. There are a large number of new, targeted therapies available and in development that have improved the therapy for patients with CLL. Patients also can benefit from non-drug preventative measures.

If you have been diagnosed with CLL, it is best to consult with a hematologist who is experienced in diagnosing, counseling and treating the disease.

This booklet tells you about the following aspects of CLL:

- Diagnosis
- Prognosis
- Treatment
- Complications

If you have additional questions about this information or about your condition, talk with your health care provider.

Words in **bold** are defined in a Glossary at the end of this booklet.

What is CLL?

CLL is a cancer of the lymphocytes, which normally work as immune cells to protect you against infections. To understand CLL, it may help you to learn some general information about your blood and immune system.

Your blood

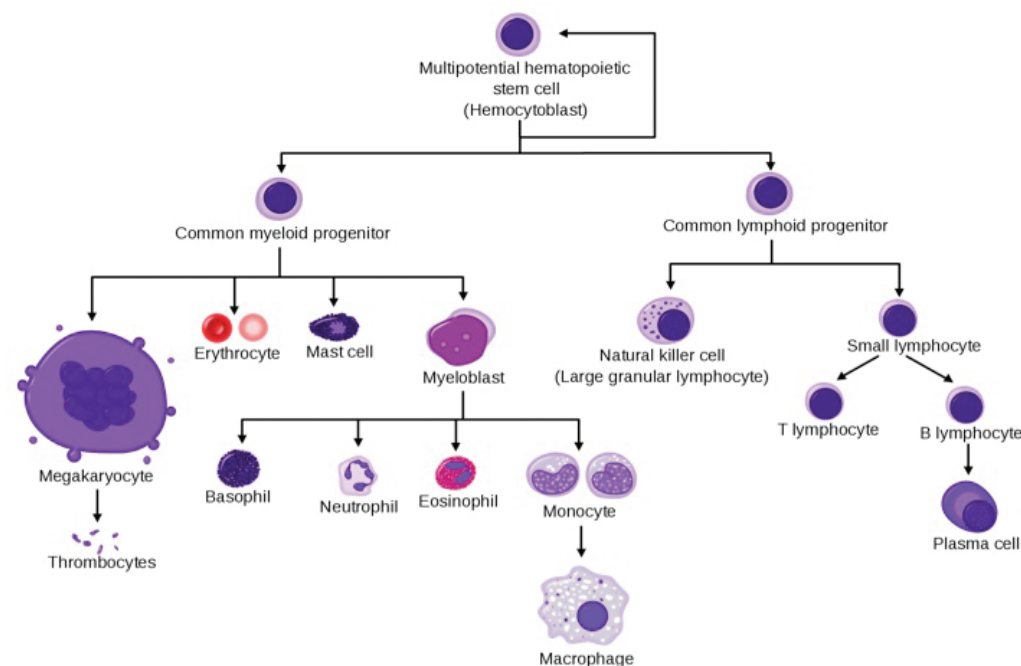
Normally, your body's bone marrow stem cells grow into different types of blood cells (figure 1), each of which has a specialized role.

- Red blood cells (erythrocytes) carry oxygen from your lungs to all parts of your body.
- Platelets prevent bleeding after an injury.
- White blood cells (leukocytes) fight infection.

In the bone marrow, stem cells mature into specific types of blood cells before being released into the bloodstream.

Figure 1. Hematopoiesis

All blood cells are derived from blood stem cells.



Lymphocytes are white cells that can recognize specific infections and generate a response that kills the infecting organisms. There are three kinds of lymphocytes:

- B lymphocytes make antibodies, specialized proteins that bind to foreign material in the body.
- T lymphocytes can kill infecting organisms, remove abnormal cells in the body, and cue the B lymphocytes to make antibodies.
- Natural killer cells are lymphocytes that destroy infected and abnormal cells.

CLL is caused when a single B-lymphocyte becomes abnormal because of damage (mutation) to its DNA. At this point, the body no longer controls this cell, so it continues to divide and lives longer than it should. This abnormal cell becomes the CLL cell.

CLL cells can gather in the bone marrow, lymph nodes, spleen and other organs, and circulate in the blood. This can result in decreased function of the bone marrow (which can result in anemia or bleeding); defects in the immune system; enlarged lymph nodes, spleen and liver; and generalized effects including fatigue, weight loss, drenching sweats, fevers, and unintended weight loss.

Figure 2a. Magnified view of blood smear from a patient with CLL. Most of the cells are normal red blood cells.

In contrast to normal blood, in which the majority of white blood cells are neutrophils that remove foreign material and kill organisms, most of these white blood cells are lymphocytes. The smaller white blood cells are intact lymphocytes (CLL cells) and cannot be distinguished from normal lymphocytes. The larger white blood cells are lymphocytes that have been broken by the process of making the blood smear. These “smudge cells” are characteristic of CLL.

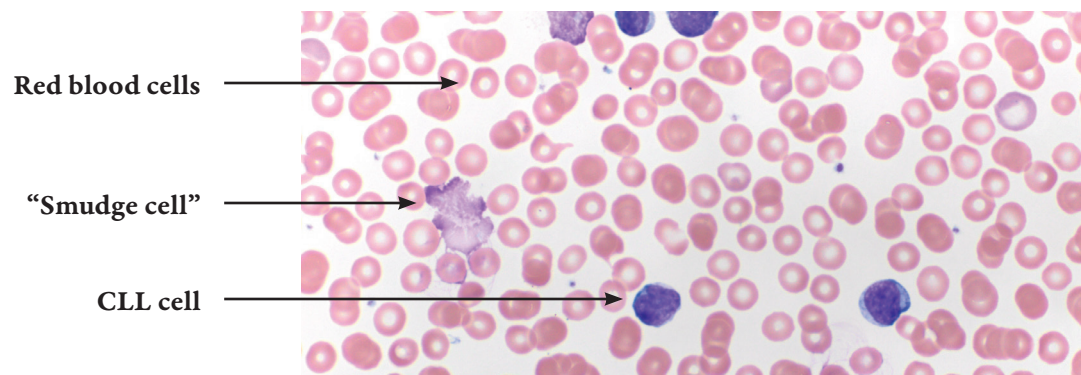
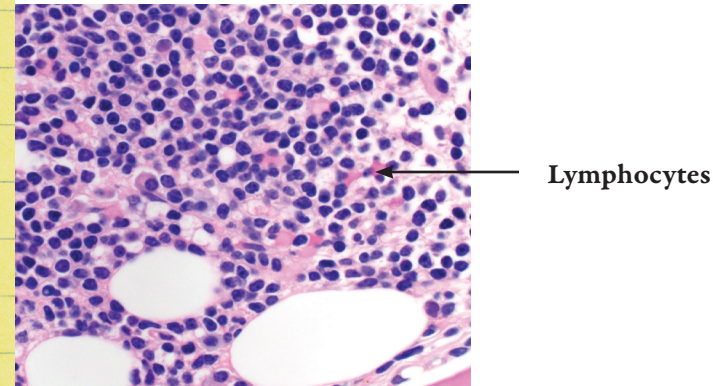


Figure 2b. Magnified view of a section of a bone marrow biopsy. The normal bone marrow cells and fat spaces have been replaced by a monotonous infiltrate of small lymphocytes (CLL cells).



What are lymph nodes?

The lymphatic system consists of ducts that drain excess body fluid from your tissues back into the veins. Lymph nodes are small organs that are found along the lymph ducts. Lymph nodes contain large numbers of white blood cells, including lymphocytes. These lymph nodes are a very important part of the normal immune system. They generate a protective immune response against any foreign material that passes through the lymphatic ducts, including infections.

Lymphocytes and other white blood cells also circulate continuously through the blood, tissues, lymphatic ducts, and bone marrow. When you have an infection, the lymphocytes in the lymph nodes respond to fight the infection and prevent further spread of disease.

When activated, lymph nodes can swell. Increased lymph node size also can be a sign of malignancy or infection. See your physician to determine the cause.

Cause/Risk Factors

The cause of CLL is not known. There is currently no scientific proof that the disease is caused by exposure to infections or toxins. However, the risk for CLL can be inherited, and some patients do have close relatives with CLL or another malignancy of B lymphocytes. People with European genetic origin also are more likely to get the disease, and men get it more often than women.

CLL is almost never found in children and rarely found in anyone under age 30. The average age of diagnosis is over 70 years.

Diagnosis and Prognosis

CLL is most often discovered after a routine blood count done for other reasons shows a high blood lymphocyte count. Some patients are diagnosed when the doctor orders tests to investigate an otherwise unexplained lymph node enlargement. Most patients are diagnosed long before they become ill from their CLL.

An accurate diagnosis is needed in order to have an idea about the likely progression of the disease (the prognosis) and the best treatment options. Your doctor also will interview you to obtain a complete medical history, and will conduct a comprehensive physical examination.

Being diagnosed with CLL can be stressful because of the potential seriousness of the disease. Talk to your health care provider about support groups and other resources available to help you and your family cope with a diagnosis of CLL.

Laboratory tests

- CBC (complete blood count). This measures the effect of CLL on normal blood cell production.
- Flow cytometric examination of blood cells. In most patients, the diagnosis can be easily confirmed with this blood test. Cells are examined with antibodies, which show if they are malignant and if they have characteristics of CLL. High levels of cellular proteins ZAP70 and CD38 may predict a poorer prognosis.

- FISH (fluorescence in situ hybridization) is a test for chromosomal abnormalities (figure 3) in the CLL cells. Some abnormalities, such as loss of part of chromosome 17, predict a more aggressive disease course.
- Gene sequencing: Sequencing of specific genes is becoming important in the management of some patients with CLL. For example, testing for mutations in the TP53 gene that codes for the p53 protein is increasingly used to choose treatment for patients with CLL. The availability of next generation sequencing technology has identified additional genes that can be evaluated to assist in determining the nature of the CLL and select treatment. These methods are being used increasingly in patient care.
- IGHV (immunoglobulin variable region of the heavy chain) mutation status. Normal B lymphocytes undergo mutations in the gene for the antibody they produce as part of the normal immune response to infection. These mutations increase the effectiveness of the antibodies. In people with CLL, the abnormal B-lymphocytes can be tested for additional mutations. More mutations of the antibody gene ($\geq 2\%$) are associated with a better prognosis.
- Bone marrow examination: This is not required to diagnose or stage CLL. A bone marrow examination is usually done before starting treatment for CLL to check the extent of disease and the cause of low blood counts.

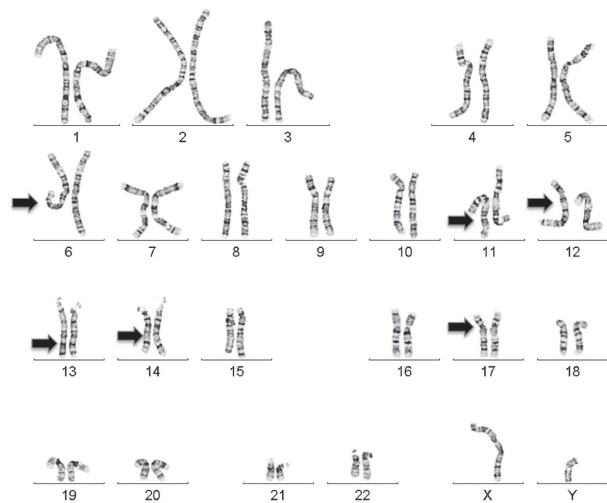


Figure 3. Chromosome defects in CLL most often affect chromosomes 6, 11, 12, 13, 14, and 17. This photograph shows the binding sites for the FISH probes used to study these chromosomes. The chromosome 14 probe is also used to ensure that patients do not have mantle cell lymphoma.

If you have been diagnosed with possible CLL, you may wish to consult with a hematologist who has experience in the diagnosis and treatment of this disease. If you have questions about tests, talk with your health care provider.

Staging

Staging is used to determine the extent of disease. This is done using the Rai classification, which divides patients with CLL into three stages: low risk, intermediate risk, or high risk. Staging depends on several factors:

- The number of affected lymph nodes on physical examination
- Spleen and liver size on physical examination
- Hemoglobin level
- Platelet counts

For patients with early and intermediate stage disease, the risk of disease progression can be predicted using the results of the genetic and other molecular measurements including FISH tests, gene sequencing, IGHV mutation analysis, and levels of CD38 and ZAP70.

Other factors, including age, sex, and overall state of health, also influence the outcome for patients with CLL. Tell your health care provider about any diseases you have (diabetes, high blood pressure, lung disease), because these may impact treatment decisions.

Treatment

Standard treatments for CLL can be very effective, but they are not cures. Treatment options change frequently, and the drugs used for therapy depend on which ones are best for each patient at the time that treatment is required.

Active Monitoring - Observation. Patients who are well and do not have any indications of CLL-related problems do not need any specific treatment. However, it is important that you follow the recommendations of your health care provider regarding follow-up and precautions. Patients who are being monitored need to stay current with appropriate vaccinations (see below), be responsive to infections, monitor for second cancers (especially of the skin) and maintain optimal general health.

Drug therapy. Chemotherapy affects the whole body, so a patient can have significant side effects. Antibody therapy is more targeted and usually has fewer side effects. Newer, more targeted drugs are now being used with success in treatment of CLL. The most effective therapies use combinations of drugs to achieve the best outcome with the least possible toxicity.

Allogeneic hematopoietic stem cell transplant (bone marrow transplant) is a treatment option for patients with aggressive CLL. This method has the potential to cure the disease. Patients are first treated with conventional therapies to reduce the amount of CLL,

and they then receive blood stem cells from a tissue-matched donor. These new blood cells replace the patient's damaged immune system, and the donor's immune system can control and prevent the recurrence of CLL.

Immune Therapy. Initial studies have shown that immune interventions (e.g. chimeric antigen receptor T cell, or CART) could be useful in the management of patients with progressive CLL. These therapies are currently considered experimental but could be available to appropriate patients on clinical trials.

Supportive care. Selected patients with CLL can benefit from supportive interventions including intravenous immunoglobulin infusions for prevention of infections, preventative antimicrobial therapy (e.g. for recurrent shingles), and blood product support as required.

Complementary therapy. People often use complementary therapies for CLL. Most of these therapies have not been formally tested, and their effectiveness and toxicities remain unknown. Some complementary therapies can interfere with other medications. To avoid possible toxic reactions, tell your health care provider if you are using any complementary therapy — especially if your CLL is being treated with conventional therapies.

Healthy Lifestyle

Healthy approaches to diet, exercise and personal habits can improve the quality of life and survival for patients with CLL.

Smoking.

Using any type of tobacco — cigarettes, snuff, pipe tobacco or cigars, and chewing tobacco — greatly increases your chance of getting cancer (e.g. lung and head and neck) and heart disease. Not using tobacco is one of the most important health decisions you can make.

Nutrition.

Follow a “heart-healthy” diet that includes low to moderate use of fat, sugar and salt, and control calorie intake to achieve and maintain a healthy weight.

Healthy food choices include the following:

- At least five fruit and vegetable servings each day
- Whole-grain and enriched cereals, breads and other foods made from whole grain
- Low-fat or skim milk and low-fat dairy products
- Lean meats, fish and poultry

Alcohol use.

Excessive alcohol use can damage your liver and other vital organs, including your bone marrow, and limit your future treatment options for CLL. Even moderate alcohol intake can have a suppressive effect on bone marrow function.

Activity.

Physical activity may help to keep your body fit. Talk to your health care provider about guidelines for an exercise program.

Hand washing.

Always wash your hands after using the bathroom, before eating and when you handle food. Wash your hands more often if you are sick or if you are around a sick person.

Screening.

CLL affects the immune system, so it increases the potential for recurrent infection and autoimmune diseases. Patients are also at increased risk for second cancers, including more aggressive lymphoma, skin cancer or solid tumors.

Follow these guidelines for cancer prevention, screening, and immunizations:

Skin.

- Use sunscreen (30 SPF or higher). Apply at least every 4 hours when exposed to the sun and after getting wet.
- Use clothing that covers the skin whenever possible.
- Avoid prolonged sun exposure.

- See a dermatologist at least once a year and whenever you see suspicious skin lesions. Check your entire skin every month, with the assistance of another person if possible.

Cancer Prevention/Surveillance.

- Discuss in detail with primary care provider at least once a year.
- Undergo all recommended check ups and tests.

Immunizations.

- Pneumovax/PPSV13 is recommended every 5 years.
- Pneumococcal Conjugate Vaccine/PCV 13 should be given once.
- Annual influenza vaccines are strongly recommended.
- Patients with CLL should not receive any live vaccines. This includes the live varicella zoster (shingles) vaccine and the live nasal flu vaccine.

Research.

Many clinical research studies are being done on CLL. Researchers design studies to better understand the causes and progression of CLL and to test the safety and effectiveness of different treatments. Some studies test treatments that have been proven, comparing them to other forms of therapy to see which ones are better. Your participation in a research project could help researchers better understand CLL, and is essential for developing better treatments for the disease.

You may be asked to participate in a clinical research study. The decision is entirely up to you. Be sure you understand the study's purpose and risks, how long it will last, and your responsibilities. Know that you can stop at any time and that is your decision — either to participate or not or to stop — in no way affects your medical care at the University of Rochester.

If you have questions about a study, speak with your health care provider.

Glossary

Antibody — A protein made by mature B-lymphocytes (plasma cells) that protects the body from infections

Autoimmune disease — Disease that occurs when your own immune system reacts against your own tissues or organs. Examples include autoimmune hemolytic anemia and immune thrombocytopenic purpura (ITP).

B lymphocyte (B-cell) — Cell made in the bone marrow that undergoes maturation in the lymph nodes and spleen to become plasma cells that make antibodies in the bone marrow.

Bone marrow — Soft tissue located in the center of the bones that produce blood cells.

Chromosome — Structure in the nucleus of a cell that is made up of DNA molecule and proteins and contains genes.

Gene — Structure within a chromosome that is responsible for the production of a specific protein. Genes determine the inheritance of a particular characteristic.

Hematologist — Specialist in diseases of the blood.

Hematopoiesis — production of blood cells in the bone marrow.

Hemoglobin — Iron-containing pigment of the red blood cell that carries oxygen to the tissues.

Lymph nodes — Organs that occur along lymphatic ducts and contain white blood cells that can react against infections.

Lymphocytes — A specialized type of white blood cell that is an essential part of the immune system.

Monotonous infiltrate — A collection of identical disease cells that invade a part of the body

Mutation — A change in the structure of the DNA of a gene that can change the protein made by that gene.

Platelet — A small blood cell that plugs up holes in blood vessels and initiates clotting.

Red blood cells (erythrocytes) — Contain hemoglobin, which carries oxygen in the blood.

Spleen — The abdominal organ that has important functions in immunity, and removes old or damaged blood cells from the circulation.

White blood cells (leukocytes) — Blood cells that prevent and control infections.





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