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The CLL Guide

Information for Patients and Caregivers

Chronic Lymphocytic Leukemia

Laura, CLL survivor

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Revised **2017**

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. Since 1954, we have invested over $1 billion in research specifically targeting blood cancers to advance therapies and save lives. We will continue to invest in research for cures, programs and services to improve the quality of life for people with chronic lymphocytic leukemia (CLL).

We know that understanding CLL can be tough.

We are here to help and are committed to provide you with the most up-to-date information about CLL, your treatment and your support options. We know how important it is for you to understand your health information and to use it with your healthcare team toward good health, remission and recovery.

Our vision is that one day all people with CLL will be cured or be able to manage their disease with good quality of life.

Until then, we trust the information in this *Guide* will help you along your journey.

We wish you well.

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

Inside This Guide

This LLS guide about CLL is for information only. LLS does not give medical advice or provide medical services.

Introduction

Chronic lymphocytic leukemia (CLL) is a type of blood cancer. This is a hopeful time for people with CLL. There are a number of treatments for CLL. In recent years, new therapies have been approved and other possible new treatments are being studied in clinical trials. Progress toward a cure is under way.

People who have CLL need to see special blood cancer doctors, called **hematologist-oncologists**.

Please use this *Guide* as a resource to help you

- Understand CLL
- Find good doctors and other healthcare providers
- Understand complicated healthcare terms
- Find and use our Information Specialists, healthcare information, booklets and resources

This *Guide* includes

- Information on how to contact our Information Specialists: call (800) 955-4572
- Links to important free LLS disease and treatment booklets: www.LLS.org/booklets
- Information about CLL treatment and care
- Simplified glossary of health terms (see page 32)
- List of suggested questions to ask the doctor (see the question guides on pages 36 and 38)

We are here to help.

Want more information?

You can view, print or order the free LLS booklet *Chronic Lymphocytic Leukemia* for more information. Go to www.LLS.org/booklets or contact our Information Specialists for a copy.

Resources and Information

LLS offers free information and services for 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 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 information about disease, treatment and support. Language services are available. For more information, please

- Call: (800) 955-4572 (Monday through Friday, 9 am to 9 pm ET)
- 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 either be 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 certain eligible patients. For more information, please

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

Community Resources and Networking

LLS Community. This is a one-stop virtual shop for chatting with other patients and staying up-to-date on the latest diagnosis and treatment news. 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 reach out and share information. 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. These resources 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 under way. Patients can learn about clinical trials and how to access them. For more information, please call (800) 955-4572 to speak with an LLS Information Specialist who can help conduct clinical-trial searches. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

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

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

Additional Help for Specific Populations

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

Language Services. Let your doctor know if you need a language interpreter or other resources, 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 (VA). For more information call the VA at (800) 749-8387 or visit www.publichealth.va.gov/exposures/agentorange.

World Trade Center 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, and those who lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA crashes

For more information, please

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

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

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

Feedback

To make suggestions about the content of this booklet, go to www.LLS.org/publicationfeedback.

Part 1

Understanding CLL

Leukemia is the general term for different types of blood cancer. Chronic lymphocytic leukemia (CLL) is one of four main types of leukemia.

About Blood

Blood is the red liquid that circulates in our bodies. It is created inside the bones, in a spongy place called the marrow.

Blood is made up of plasma and blood cells.

Plasma. This is the liquid part of the blood. It is mostly water. It also has some vitamins, minerals, proteins, hormones and other natural chemicals.

Blood cells. Each blood cell starts as a stem cell. Then it becomes one of three types of blood cells:

- Blood platelets (allow blood to clot)
- White blood cells (fight infection)
- Red blood cells (carry oxygen)

Normal Blood Cell Count Fast Facts

The ranges of blood cell counts below are for adults. They may be a little different from lab to lab and for children and teens.

Red blood cell (RBC) count

- Men: 4.5 to 6 million red cells per microliter of blood
- Women: 4 to 5 million red cells per microliter of blood

Hematocrit (the part of the blood made up of red cells)

- Men: 42% to 50%
- Women: 36% to 45%

Hemoglobin (amount of the red cell pigment that carries oxygen)

- Men: 14 to 17 grams per 100 milliliters of blood
- Women: 12 to 15 grams per 100 milliliters of blood

Platelet count (PLAT C)

- 150,000 to 450,000 platelets per microliter of blood

White blood cell (WBC) count

- 4,500 to 11,000 white cells per microliter of blood

Differential (also called **diff**)

- Shows the part of the blood made up of different types of white cells
- The types of white cells counted are neutrophils, lymphocytes, monocytes, eosinophils and basophils.
- Adults usually have about 60% neutrophils, 30% lymphocytes, 5% monocytes, 4% eosinophils and less than 1% basophils in the blood.

The Immune System

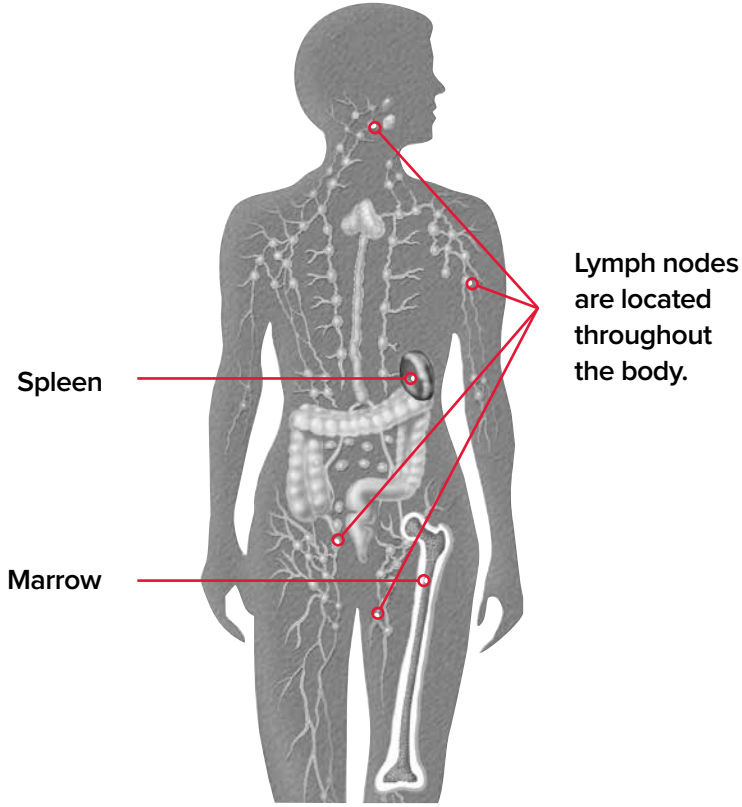
The immune system is the body's defense against infection.

The marrow and the lymphocytes are part of the immune system. A lymphocyte is a type of cell that fights infection. Here are some other parts of the immune system:

Lymph nodes are bean-sized collections of lymphocytes throughout the body. There are about 600 lymph nodes—in the neck, armpits, chest, abdomen, groin and other body parts. Lymphatic vessels connect the lymph nodes. They contain lymph, a fluid that carries lymphocytes.

The spleen is an organ on the left side of the body, near the stomach. It contains lymphocytes and removes worn-out cells from the blood.

Some Parts of the Immune System



What is CLL?

CLL is a type of cancer that begins in the bone marrow. It starts with a change to a lymphocyte (the type of cell that fights infection). But CLL cells do not fight infection like normal lymphocytes do.

Over time, the uncontrolled growth of CLL cells in the marrow leads to an increase in the number of CLL cells in the blood. The leukemic cells that accumulate in the marrow in people with CLL do not prevent normal blood cell production as much as with acute leukemia.

Some people have CLL that grows slowly. They do not need drug therapy right away. Other people have CLL that grows more quickly. They do need drug therapy once their CLL is diagnosed. (Information about treatment begins on page 14.)

Causes of CLL. Doctors do not know what causes the cell change that leads to CLL.

- There is no way to prevent CLL.
- You can not catch CLL from someone else.
- It is not common, but in some families, more than one blood relative has CLL. Doctors are studying why some families have a higher rate of CLL.
- Some studies have associated exposure to Agent Orange, an herbicide used during the Vietnam War, with an increased risk of CLL (see *Information for Veterans* on page 5).

Children do not get CLL. It is not a common disease in adults. The number of people with CLL starts to increase after age 50. A small number of people are diagnosed with CLL in their 30s and 40s.

Signs and Symptoms

Healthy people often get a "sign" or a "symptom" when they get an illness or a disease.

- A sign is a change in the body that the doctor sees in an exam or a test result.
- A symptom is a change in the body that the patient can see or feel.

Some people with CLL have no symptoms. These people may find out they have CLL after a regular medical checkup shows certain changes in the blood. CLL symptoms often develop slowly. People with CLL may have little or no change in their health for many years.

Some Signs and Symptoms of CLL

Tiring more easily	People may have less energy due to fewer healthy red blood cells and more CLL cells.
Shortness of breath	People may have shortness of breath while doing usual day-to-day activities. This is due to fewer healthy red blood cells and more CLL cells.
Swollen lymph nodes or spleen	High numbers of CLL cells can gather in the lymph nodes or spleen as the number of CLL cells increases.
Infections	People with a very high number of CLL cells in the marrow may have repeated infections. This is because CLL cells cannot fight off infection as well as healthy lymphocytes.
Weight loss	Some people with CLL lose weight because they eat less and/or because they are using more energy.

People with CLL sometimes have other symptoms, such as fever or night sweats. Many people who do not have CLL may have some of the signs and symptoms of the disease. Because a number of illnesses have signs and symptoms similar to those of CLL, it is important to have your doctor figure out the cause of your symptoms. This will probably begin with a blood test.

Diagnosing CLL

The doctor orders blood tests when a person has a high lymphocyte count. Your blood may be drawn in the doctor's office or in a hospital and sent to a lab.

Blood Tests. The testing for CLL includes blood cell counts and a blood cell examination.

- **Blood cell counts.** The doctor orders a lab test called a **complete blood count (CBC)** to check the numbers of blood cells. A person with CLL usually has a high number of lymphocytes (high lymphocyte count). He or she may also have a low red blood cell count and a low platelet count.
- **Blood cell examination.** The CLL cells are usually examined with an instrument called a flow cytometer. The test is called **flow cytometry** or **immunophenotyping**. This is done to find out if CLL is the reason for the high lymphocyte count. Flow cytometry also shows the type (B-cell or T-cell) of CLL. B-cell CLL is the most common type.

Other lab tests for CLL include:

Immunoglobulin Test. Doctors check the immunoglobulin level in the blood. Immunoglobulins are proteins that help the body fight infection. People with CLL may have low levels of immunoglobulins. A low immunoglobulin level may be the cause of repeated infections. People who have low immunoglobulin levels and repeated infections may be given injections (shots) of immunoglobulins.

Bone Marrow Tests. Bone marrow tests are not usually needed to make a CLL diagnosis. But it is often helpful to have a bone marrow aspiration and a bone marrow biopsy before treatment begins.

The results of these tests serve as a baseline that is used later on to assess the effects of treatment. These tests are almost always done together.

Often patients are awake during the procedure. They are given medication to their hip bone to numb the biopsy and aspiration site. Once that area of the body is really numb, the bone marrow samples are taken using a special needle. Some patients are sedated (asleep) for the procedure.

How Are Blood and Bone Marrow Tests Done?

Blood tests	Usually a small amount of blood is taken from the person's arm with a needle. The blood is sent to a lab.
Bone marrow aspiration	A liquid sample of cells is taken from the marrow through a special needle. The cells are then looked at under a microscope.
Bone marrow biopsy	A very small amount of bone filled with marrow cells is removed through a special needle. The cells are then looked at under a microscope.

FISH. A test called **fluorescence in situ hybridization (FISH)** is used to see if there are changes to the chromosomes of the CLL cells. Every cell in the body has chromosomes that carry genes. Genes give the instructions that tell the cell what to do. More than half the people with CLL have CLL cells with chromosome changes. FISH may give doctors information that will tell them which people with CLL need more medical follow-up care (see page 17). A patient may need different treatments as a result of the FISH test. FISH can be done with a sample of cells from blood or marrow.

Tracking Your CLL Tests

These tips may help you save time and learn more about your health.

- Ask your doctor why certain tests are being done and what to expect.
- Discuss test results with your doctor.
- Ask for and keep copies of lab reports in a file folder or three-ring binder. Organize test reports in order by date.
- Find out if and when follow-up tests are needed.
- Mark upcoming appointments on your calendar.

Want more information?

You can view, print or order the free LLS booklet *Understanding Lab and Imaging Tests* to learn more about lab tests and what to expect. Go to www.LLS.org/booklets, or contact our Information Specialists for a copy.

Part 2

Treating CLL

Finding the Right Doctor

Patients with CLL are treated by special doctors called **hematologist-oncologists** that understand cancer and the blood. You may want to consider seeing a hematologist-oncologist who specializes in CLL.

Finding the right doctor, one that you like and feel comfortable with, is important. Refer to these resources to help you find the right cancer specialist

- Your primary care doctor
- The community cancer center
- Your health plan and its referral services

- Online doctor-finder resources, such as
  - The American Medical Association's (AMA) "DoctorFinder"
  - The American Society of Hematology's (ASH) "Find a Hematologist"
- LLS resources such as our Information Specialists, who can be reached from Monday to Friday 9 am to 9 pm ET at (800) 955-4572

Your doctor will help you understand CLL and create a treatment plan. When you meet with your doctor

- Ask questions
  - Use the question guides on pages 36 and 38 to help.
  - You can call an Information Specialist to help create or modify questions before you see a doctor.
  - Read and print other LLS "What To Ask" question guides at www.LLS.org/whattoask.
- Take notes or bring an audio recorder to record your visits.
- Bring a friend or family member to help you understand and take notes.
- Make sure you understand what the doctor is saying. If you don't, ask the doctor to explain things so you can understand.
- If you need more information, consider getting another opinion (a second opinion).

Want more information?

You can view, print or order the free LLS booklet *Choosing a Blood Cancer Specialist or Treatment Center* at www.LLS.org/booklets. For a list of questions to ask your doctor, see the question guides on pages 36 and 38. You can also access and print question guides about second opinions and other topics at www.LLS.org/whattoask. Or contact our Information Specialists for copies.

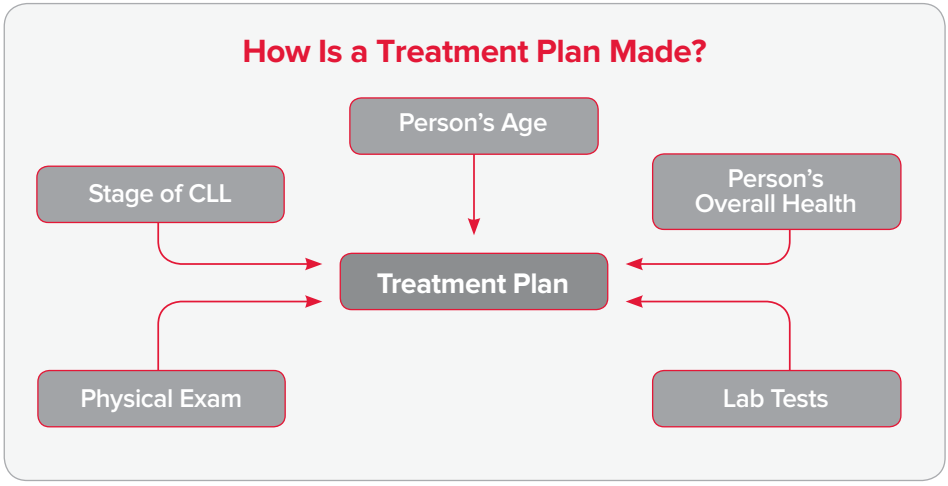
Treatment Planning

The goals of CLL treatment are to

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

The treatment plan for a person with CLL depends on the

- Stage of CLL (low-risk, intermediate-risk or high-risk) (see page 17)
- Physical exam and lab test results
- Person's overall health
- Person's age (for some treatments)



CLL Staging. Many doctors use a system called **staging** to help plan treatment for people with CLL. Many doctors use the **Rai staging system**, which defines a person's risk as follows:

- **Low-Risk CLL**
  - High lymphocyte count in the blood and the marrow
- **Intermediate-Risk CLL**
  - High lymphocyte count in the blood and the marrow and enlarged (swollen) lymph nodes

    or
  - High lymphocyte count in the blood and the marrow and enlarged (swollen) liver and/or spleen
- **High-Risk CLL**
  - High lymphocyte count in the blood and the marrow and anemia (low red blood cell count)

    or
  - High lymphocyte count in the blood and the marrow and low platelet count

Lab test results may show signs of faster-growing disease (higher-risk CLL). This means the person needs closer follow-up with the doctor.

Chromosome Changes. The doctor will use FISH and other tests to identify chromosome changes. Knowing that a patient has chromosome changes can also help the doctor figure out the best treatment option. The following are some of the chromosome changes your doctor will be testing for.

- **Del(13q).** Part of chromosome 13 is missing—this means that a person has a slightly better outcome.
- **Trisomy 12.** There are three copies of chromosome 12—this means that the person needs closer follow-up.
- **Del(11q).** Part of chromosome 11 is missing—this means that the person needs closer follow-up.

- **Del(17p).** Part of chromosome 17 is missing—this means that the person needs closer follow-up. Speak to your doctor about your treatment options, because this mutation requires a different treatment plan (see page 24).

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

Blood Lymphocyte Doubling Time. A lymphocyte number that doubles in one year means that the person needs closer follow-up.

Beta$_2$-Microglobulin (B$_2$M). B$_2$M is a protein on CLL cells. A higher level of B$_2$M may mean there are more CLL cells.

Under Study. A factor called **ZAP-70** may give doctors information about a person's response to treatment. When ZAP-70 factor is increased, this may be associated with higher-risk disease.

Want more information?

You can view, print or order the free LLS booklet *Chronic Lymphocytic Leukemia* to learn more about factors under study and other detailed information about CLL. Go to www.LLS.org/booklets or contact our Information Specialists for a copy.

Treatments for CLL

Current therapies do not offer patients a cure for CLL, but there are treatments that help manage the disease. Treatments for CLL include

- Watch and wait
- Chemotherapy
- Targeted therapies
- Monoclonal antibody therapies
- Supportive care

- Stem cell transplantation
- Treatment in a clinical trial (see page 26)

Watch and Wait is a treatment approach that means a doctor will observe a person's condition during physical exams and will order lab tests. The doctor does not treat the person with drugs or other therapies during the watch and wait period.

People with CLL may think they should have treatment right away. But for people with low-risk (slow-growing) disease and no symptoms, it is often best not to start treatment. With a watch and wait approach, the person avoids the side effects of therapy until it is needed. Many studies have compared the watch and wait approach to early treatment for people with low-risk CLL. This is also an area of ongoing study in clinical trials. To date, no benefits of early treatment for people with low-risk CLL have been shown.

A person with CLL being monitored with the watch and wait approach needs follow-up visits with the doctor. At each office visit the doctor will check for any health changes. If you notice that you are having a number of infections, increasing fatigue or significant loss of well-being, you should contact your doctor for guidance. You do not need to wait for your next appointment. This is a partnership and your doctor is counting on you to report if anything has changed.

The results of exams and lab tests over time will help the doctor advise the person about

- When to start treatment
- The type of treatment to receive

Treatment will begin if there are signs or a person develops symptoms showing that the CLL is starting to grow. The doctor may advise a person to begin treatment if one or more of the following signs develop:

- The number of CLL cells increases
- The number of healthy cells decreases

- The number of red blood cells decreases
- The number of platelets decreases
- The lymph nodes have become larger
- The spleen/liver has become larger
- CLL symptoms begin, which include
  - Fatigue
  - Night sweats
  - Unexplained weight loss
  - Low-grade fever

A person with any or all of these signs or symptoms may start to feel too tired for normal daily activities.

Chemotherapy is treatment with drugs that kill or damage cancer cells. Some drugs are given by mouth. Other drugs are given through a vein (intravenously, or IV) by placing a small needle in the arm. Two or more drugs are often used together. The FDA-approved drugs fludarabine (Fludara®), cyclophosphamide (Cytoxan®), bendamustine hydrochloride (Bendeka®) and other standard chemotherapies are used to treat people with CLL. For a list of drugs used to treat CLL, see page 21. Information about side effects of treatment for CLL starts on page 27.

Targeted therapies target specific substances on the cancer cell. Most targeted therapy drugs for CLL are given as pills and in general have milder side effects than chemotherapy. Ibrutinib (Imbruvica®) was the first targeted therapy approved for CLL. Other options include idelalisib (Zydelig®) and venetoclax (Venclexta®). In some cases, drugs approved for other blood cancers, such as lenalidomide (Revlimid®), are used to treat CLL. Future clinical trials will determine in which order these drugs are used in treating patients.

Monoclonal antibody therapies are treatments that use immune-system proteins (antibodies) that are made in the lab.

Monoclonal antibody therapies aim for a specific target on the surface of the CLL cells. The antibody attaches to the cell and then the cell dies. Monoclonal antibody therapies do cause some side effects. In general, the side effects are milder than the side effects of chemotherapy (see page 27).

Rituximab (Rituxan®), obinutuzumab (Gazyva®), alemtuzumab (Campath®), ofatumumab (Arzerra®), and rituximab and hyaluronidase human (Rituxan Hycela™) are five FDA-approved monoclonal antibody therapies used to treat people with CLL. With the exception of Rituxan Hycela, which is given subcutaneously (sub-q), the rest of these therapies are given intravenously (through an IV line). Other new monoclonal antibodies to treat people with CLL are being studied in clinical trials.

Drugs Used to Treat CLL

Chemotherapy	Bendamustine HCl (Bendeka®) Chlorambucil (Leukeran®) Cladribine (Leustatin®) Cyclophosphamide (Cytoxan®) Doxorubicin (Adriamycin®, Rubex®) Fludarabine (Fludara®) Prednisone
Targeted Therapy	Ibrutinib (Imbruvica®) Idelalisib (Zydelig®) Lenalidomide (Revlimid®) Venetoclax (Venclexta®)
Monoclonal Antibody Therapy	Alemtuzumab (Campath®) Ofatumumab (Arzerra®) Obinutuzumab (Gazyva®) Rituximab (Rituxan®) Hyaluronidase human (Rituxan Hycela™)

Supportive Care. Supportive care is given to prevent or treat CLL symptoms and/or treatment side effects. Supportive care for CLL may include

- **Antibiotics to treat infections caused by bacteria or fungi.** Infections are a risk for people with CLL. Treatment for CLL lowers the number of infection-fighting white blood cells. People with repeat infections may also get injections (shots) of immunoglobulin (gamma globulin).

- **Vaccinations.** Due to the high risk of infections in CLL patients, immediate vaccination for pneumococcal pneumonia with Prevnar 13® (repeated every 5 years) and a yearly flu vaccination is recommended. CLL patients should never receive live vaccines (including the shingles vaccine).

- **Blood transfusions or red blood cell growth factors to increase the red blood cell count.** Anemia (low numbers of red blood cells) is a common side effect of chemotherapy. Examples of red blood cell growth factors are darbepoetin alfa (Aranesp®) and epoetin alfa (Procrit®).

- **Growth factors to improve low white blood cell counts.** CLL-related low white blood counts are often corrected by CLL therapy. Sometimes the use of white blood cell growth factors can help people with CLL who have a long period of low white blood cell counts after treatment. Examples of white blood cell growth factors are filgrastim (Neupogen®) or pegfilgrastim (Neulasta®) (also called **G-CSF**) and sargramostim (Leukine®) (also called **GM-CSF**).

  Blood cell growth factors may help the patient tolerate the side effects of higher doses of chemotherapy. People with CLL should discuss the risks and benefits of treatment using blood cell growth factors with their doctors.

- **Radiation Therapy.** This treatment uses x-rays or other high-energy rays to kill cancer cells. Radiation therapy is sometimes used to treat a person with CLL who has an enlarged (swollen) lymph node, spleen or other organ that is blocking the function of a neighboring body part, such as the kidney or the throat. This therapy is rarely used for CLL.

- **Splenectomy.** The spleen is an organ on the left side of the body, near the stomach. CLL cells can enlarge the spleen and cause discomfort in some people with CLL. Also, an enlarged spleen may lower the person's blood cell counts to dangerous levels. An operation to remove the spleen is called a **splenectomy**. Splenectomy is helpful for some people with CLL if the spleen is very enlarged as a result of the disease. The operation may improve the person's blood cell counts.

Treatment Options. CLL treatment is changing and treatment options vary by age.

CLL Patients Younger Than 65 to 70 Years Without del(17p). Two or more drugs are often combined to treat people with CLL who need drug therapy. Fludara is often combined with other drugs. For example

- FC – Fludara, Cytoxan
- FR – Fludara, Rituxan
- FCR – Fludara, Cytoxan, Rituxan

Studies have compared treatment of Fludara alone or FC with FR or FCR. These have shown that FR or FCR treatment improves how often untreated patients achieve complete remission and overall survival. Fludara combined with other drugs is being studied in clinical trials.

CLL Patients Older Than 65 to 70 Years Without del(17p). Older patients represent the most common group of patients with CLL and studies have not shown much benefit with Fludara-based treatment. Some combinations for treatment that improve response rate and remission duration include

- Leukeran plus Rituxan
- Leukeran plus Arzerra (has shown prolonged survival when combined with Leukeran)
- Leukeran plus Gazyva (has shown prolonged survival when combined with Leukeran)

Both combinations of Leukeran plus Arzerra and Leukeran plus Gazyva have been approved for first-line treatment of CLL patients.

CLL Patients With del(17p). Young and older patients with del(17p) do not respond well to any type of chemotherapy or monoclonal antibody treatment. These patients are best directed toward

- Clinical trials
- Novel therapies such as Imbruvica and Venclexta
- Allogeneic stem cell transplant

Stem Cell Transplantation

Your doctor will talk to you about whether stem cell transplantation is a treatment option for you.

Allogeneic Stem Cell Transplantation. This is a procedure that uses stem cells from a donor. The donor may be a brother or sister. Or the donor can be an unrelated person with stem cells that "match" the patient's. Stem cells may also come from one or more donor cord blood unit(s) (the blood in the umbilical cord after a baby's birth).

The goals of an allogeneic transplant are to

- Restore the body's ability to make healthy blood cells after high-dose chemotherapy
- Kill the remaining CLL cells in the patient's body

This procedure may be done in the hospital. Stem cells are collected from a donor. Before the transplant, the person receives CLL drug therapy to bring the disease under control. After the person responds to this treatment, the patient is given high-dose chemotherapy and/or radiation therapy. The donor stem cells are given to the patient through an IV (intravenous) line or central line. The donor stem cells go from the patient's blood into the marrow. They help to start a new supply of healthy red blood cells, white blood cells and platelets.

An allogeneic stem cell transplantation has a high risk of serious complications. Your doctor will explain the benefits and the risks if transplantation is suggested for you.

Doctors are working to make allogeneic stem cell transplants safer. A type of transplant called a **reduced-intensity transplant** uses lower doses of chemotherapy than a standard allogeneic stem cell transplant. This treatment is also called a **nonmyeloablative** transplant. Older and sicker people may be helped by this treatment.

Want more information?

You can view, print or order the free LLS booklet *Blood and Marrow Stem Cell Transplantation* for more information. Go to www.LLS.org/booklets or contact our Information Specialists for a copy.

Treatment for Relapsed or Refractory CLL

Relapsed CLL is the term for CLL that at first responded to therapy, but then stopped responding six or more months after therapy.

Refractory CLL is the term used to describe CLL that either

- Does not result in a remission but may be stable
- Does not result in a remission and gets worse within six months of the last treatment

It is important to have another FISH test prior to additional treatments because this test can help your doctor determine the next therapy. New mutations can develop over time or as a result of past treatments.

There are now many treatment options for people with CLL. People who are treated for relapsed or refractory CLL often have good quality years of remission after more treatment.

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 20 for more information about these treatments.

New knowledge should emerge in the near future about how to best treat patients who relapse. Relapsed patients should speak to their doctor about joining a clinical trial.

Part 3

About Clinical Trials

Doctors may recommend that a patient join a clinical trial. Clinical trials are careful studies done by doctors to test new drugs or treatments, or test new uses for approved drugs or treatments. For example, changing the amount of the drug or giving the drug along with another type of treatment might be more effective. Some clinical trials combine drugs for CLL in new sequences or dosages.

There are clinical trials for

- Patients newly diagnosed with CLL
- Patients who did not get a good response to treatment
- Patients who relapsed after treatment

A carefully conducted clinical trial may provide the best available therapy. Ask your doctor if treatment in a clinical trial is right for you. Some drugs being studied in clinical trials are listed in *Drugs Used to Treat CLL* on page 21. There are also other approaches to treating CLL. You can call our Information Specialists for information about clinical trials. When appropriate, personalized clinical trial navigation by trained nurses is also available.

Want more information?

You can view, print or order the free LLS booklet *Knowing All Your Treatment Options* at www.LLS.org/booklets, or contact our Information Specialists for a copy.

Part 4

Side Effects and Treatment Response

Side Effects of CLL Treatment

The term **side effect** is used to describe an unplanned result of treatment, usually something unpleasant or not desirable.

People react to treatments in different ways. Sometimes they have mild side effects. Other side effects may be serious and last a long time. Most side effects go away when treatment ends.

Some possible side effects of CLL treatment include

- Achy feeling
- Diarrhea
- Constipation

- Extreme tiredness
- Hair loss
- Infections
- Low blood pressure
- Low platelet count (thrombocytopenia)
- Low red blood cell count (anemia)
- Low white blood cell count (leukopenia)
- Mouth sores
- Upset stomach and vomiting

Talk to your doctor about the possible side effects and long-term effects of your treatment. You can also call our Information Specialists.

Want more information?

You can view, print or order the free LLS booklet *Understanding Side Effects of Drug Therapy* for more information. Go to www.LLS.org/booklets or contact our Information Specialists for a copy.

Treatment Response

People with CLL have a range of responses after treatment. Talk to your doctor about the results and the goals of your treatment. Your doctor may use the following terms to talk about response to treatment.

- **Remission.** No sign of disease; sometimes the terms complete remission (or complete response) or partial remission (or partial response) are used

- **Complete Response (CR).** No sign of disease for at least two months after the end of treatment; normal blood counts and hemoglobin greater than 11 grams per deciliter (g/dL) without transfusions; no CLL signs or symptoms

- **Partial Response (PR).**
  - At least a 50 percent reduction in
    - Number of blood lymphocytes
    - Lymph node and spleen enlargement
  - One or more of the following maintained for at least two months:
    - Platelets greater than 100,000 platelets per microliter (µl) of blood
    - Hemoglobin greater than 11 g/dL
    - A 50 percent improvement over pretreatment red blood cell or platelet counts without transfusions

- **Stable Disease.** The patient's CLL is not growing, but the person does not have a complete or partial response

- **Progressive Disease.** The signs of progressive disease are at least one of the following:
  - An increase of at least 50 percent in lymphocyte count or other signs of high-risk CLL. Lymphocytosis (high lymphocyte count) can be temporarily seen with Imbruvica and Zydelig and do not indicate disease progression in the absence of other signs.
  - An increase of at least 50 percent in liver or spleen size or a newly enlarged liver or spleen
  - An increase of at least 50 percent in the combined size of at least two lymph nodes, in two exams in a row, done two weeks apart
  - Appearance of new enlarged lymph nodes

Follow-Up Care

After CLL treatment, people need to see their primary care doctor and oncologist for follow-up care. At these visits, the doctor will check you and learn how you are doing. Blood tests, bone marrow tests or FISH may be needed from time to time to evaluate your treatment progress and to decide if more treatment is needed. The doctor may recommend longer periods of time between visits if a person continues to be free of CLL signs or symptoms; however, follow-up visits should be ongoing.

Minimal Residual Disease (MRD). Some people with CLL have a very low level of remaining CLL cells after treatment. The remaining CLL cells are called **minimal residual disease** (MRD). MRD cannot be detected by the usual blood and marrow tests. The tests to detect MRD in people with CLL are **four-color flow cytometry** and **polymerase chain reaction (PCR)**. These tests may help the doctor identify the need for more treatment.

For each follow-up visit:

- Track each visit and record what was discussed.
- Ask your doctor if and why certain tests are being done and what to expect.
- Discuss test results with your doctor.
- Ask for and keep copies of lab reports in a file folder or binder.
- Organize the reports in order by date.
- Find out if and when follow-up tests are needed.
- Mark upcoming appointments on your calendar.

Ongoing Care

It is very important that you take very good care of yourself. Review the following tips to keep yourself healthy and happy.

- Keep all doctors' appointments.
- Talk about how you feel with the doctor at each visit.
- Ask any questions you may have about side effects.
- People with CLL may have more infections. Follow the doctor's advice for preventing infection.
- Eat healthy foods each day. It is okay to eat four or five smaller meals instead of three bigger ones.
- Contact the doctor about tiredness, fever or other symptoms.
- Do not smoke. Patients who smoke should get help to quit.
- Get enough rest.
- Exercise, but first talk with your doctor before starting an exercise program.
- Keep a healthcare file with copies of lab reports and treatment records.
- Have regular cancer screenings.
- See your primary care doctor to keep up with other healthcare needs.
- Talk with family and friends about how you feel. When family and friends know about CLL and its treatment, they may worry less.
- Seek medical advice if you feel sad or depressed and your mood does not improve over time. If you feel sad or depressed every day for a two-week period, seek help. Depression is an illness. It should be treated even when a person is being treated for CLL. Treatment for depression has benefits for people living with cancer.

Health Terms

Antibiotics. Drugs that are used to treat infections caused by bacteria and fungi. Penicillin is one type of antibiotic.

Antibodies. Proteins made by plasma cells. Antibodies help fight infection in the body.

Baseline testing. Tests that are used to get information before treatment, which will be compared to information in test results after treatment.

Beta$_2$-microglobulin (B_2M). A cell protein that enters the blood. Measuring the amount of this cell protein can be one way to assess a person's type of CLL. A high level of B_2M may mean the CLL is a faster-progressing type of CLL.

Bone marrow aspiration. A procedure to remove and examine marrow cells to see if they are normal. A liquid sample containing cells is taken from the marrow and then the cells are looked at under a microscope.

Bone marrow biopsy. A procedure to remove and examine marrow cells to see if they are normal. A very small amount of bone filled with marrow cells is taken from the body, and the cells are looked at under a microscope.

Chemotherapy or drug therapy. Use of chemical agents to treat CLL and other diseases.

Chromosomes. Any of the 23 pairs of certain basic structures in human cells. Chromosomes are made up of genes. Genes give the instructions that tell each cell what to do. The number or shape of chromosomes may be altered by the disease in blood cancer cells.

Clinical trials. Careful studies done by doctors to test new drugs or treatments, or to test new uses for already approved drugs or treatments.

The goal of clinical trials for blood cancers is to improve treatment and quality of life and to find cures.

Combination chemotherapy or drug therapy. The use of two or more drugs given at the same time to treat CLL and other diseases.

Diagnose. To detect a disease from a person's signs, symptoms and lab test results. The doctor diagnoses a patient.

FDA. The short name for the US Food and Drug Administration. Part of the FDA's job is to assure the safety and security of drugs, medical devices, and the US food supply.

FISH. The short name for fluorescence in situ hybridization, a test that measures the presence of a specific chromosome or gene in the cells. The results of this test can be used to plan treatment and to measure the results of treatment.

G-CSF. The short name for granulocyte-colony stimulating factor, a natural substance that stimulates the growth of neutrophils (a type of white cell that fights infection). Chemotherapy kills cancer cells, but also decreases the number of neutrophils in the blood and marrow. G-CSF that is made by genetic engineering (Neupogen® and Neulasta®) may be used to treat or prevent a low neutrophil count.

GM-CSF. The short name for granulocyte macrophage-colony stimulating factor, a natural substance that stimulates the growth of macrophages and other white blood cells that fight infection. Chemotherapy kills cancer cells, but it also decreases the number of macrophages and other white blood cells in the blood and marrow. GM-CSF that is made by genetic engineering (Leukine®) is used to treat or prevent a low white blood cell count.

Hematologist. A doctor who specializes in treating blood cell diseases.

Immune response. The reaction of the body to foreign material. Examples of foreign material are an infection-causing micro-organism,

a vaccine, or the cells of another person used for an allogeneic stem cell transplant.

Immune system. Cells and proteins in the body that defend it against infection.

Immunoglobulins. Proteins that fight infection.

Immunotherapy. The treatments used to boost the body's immune system.

Lymphocyte. A type of white blood cell that is part of the immune system and that fights infection.

Marrow. The spongy material in the center of bones where blood cells are made.

Monoclonal antibody therapy. Immune proteins made in a laboratory. This therapy targets and kills specific cancer cells. It does not cause many of the side effects of chemotherapy.

Oncologist. A doctor who specializes in treating patients who have cancer.

Pathologist. A doctor who specializes in identifying diseases by studying cells and tissues under a microscope.

PCR. The short name for polymerase chain reaction, a sensitive lab test that can measure the presence of cancer cell-markers in the blood or marrow. PCR is used to detect cancer cells that may remain after treatment but that cannot be detected by other tests.

Plasma. The clear liquid part of the blood (red blood cells make blood look red).

Platelet. A type of blood cell that helps prevent bleeding. Platelets cause plugs to form ("clot") in the blood vessels at the site of an injury.

Red blood cell. A type of blood cell that carries oxygen to all parts of the body. In healthy people, red blood cells make up almost half of the blood.

Refractory CLL. CLL that has not responded to initial treatment. Refractory disease may be disease that is getting worse or staying the same (stable disease).

Relapsed CLL. CLL that responded to treatment but then returns.

Remission. No sign of the disease and/or a period of time when the disease is not causing any health problems.

Stem cell. A type of cell found in marrow eventually becomes a red blood cell, a white blood cell, a platelet, or another kind of cell.

White blood cell. A type of cell in blood that helps the body fight infection.

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Questions to Help You **Choose a Specialist**

Asking questions will help you take an active role in managing your (or your child's) care. If you do not understand any part of the information your healthcare provider gives you, ask him or her to explain it in another way.

Doctor's name _____

Date of appointment or call _____

1. What is your board certification and licensing? Are you a member of any professional societies?

_____

_____

2. How much experience do you have treating patients who have my disease?

_____

_____

3. Is your hospital, university, center or clinic accredited and experienced in treating blood cancers?

_____

_____

4. How long would I usually have to wait for appointments or return of my phone calls?

_____

_____

5. Will there be nurses, social workers and case managers available to help me with support needs and quality-of-life concerns?

_____

_____

6. Do you know of other oncologists who specialize in treating blood cancers? Would you recommend that I speak to any of them?

_____

_____

7. What types of things should I call you about? What types of things should I call my family doctor about?

_____

_____

8. How should I contact you when I have questions?

_____

_____

9. How do I contact you at night? On weekends? On holidays?

_____

_____

To print additional copies of this question guide, or to print copies of question guides on other topics, go to www.LLS.org/whattoask. You may also request that copies be sent to you by contacting our Information Specialists at (800) 955-4572.

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Questions to Ask Your **Healthcare Provider About Treatment**

Asking your healthcare provider questions at any phase of your treatment will help you take an active role in managing your (or your child's) care. If you do not understand any part of the information your healthcare provider gives you, ask him or her to explain it in another way.

Doctor's name _____

Date of appointment or call _____

1. What are my (my child's) treatment options? What is the goal of the treatment?

_____

_____

2. What are the FDA-approved treatments, and are there treatments being studied in clinical trials (study treatments), for my (my child's) diagnosis?*

_____

_____

3. What are the benefits and risks of the treatment(s) available to me (my child)? What are the expected side effects?

_____

_____

4. Is there one treatment option (FDA-approved or study treatment) that you recommend over the others? Please explain.

_____

_____

5. If I (my child) enroll(s) in a clinical trial, who will be in charge of my (my child's) treatment?

6. When do you think I (my child) will need to begin treatment?

7. How long will I (my child) be treated and how many treatments will be needed?

8. Will I (my child) need to be hospitalized for all or part of the treatment?

9. What kind of testing will be done to monitor my (my child's) disease and treatment? How often will testing be needed?

10. If I am treated at an out-patient clinic or at the doctor's office, will I be able to drive/get myself home after treatments or will I need someone to assist me?

11. What are the risks if I don't (my child doesn't) get treatment?

12. How will I know if the treatment is effective? What options are available if the treatment is not effective?

_____

_____

13. How do I find out if my insurance will cover the costs of my (my child's) treatment or the study treatment? Who can help answer any medical questions my insurance company or health plan asks?

_____

_____

14. If I do not have insurance coverage, how can the healthcare team help me (my child) get treatment? Is there someone I need to speak to for assistance?

_____

_____

15. If I'm (my child is) getting a study treatment, will I be responsible for paying any treatment-related costs, such as tests, travel or the clinical trial drug(s)?

_____

_____

16. Will the healthcare team continue to check on me (my child) after the treatment is over? If so, for what period of time?

_____

_____

17. I (My child) would like to continue some type of lifelong follow-up care in order to be monitored for long-term and late effects of treatment. Can I (my child) follow up with you?

_____

_____

*For definitions of an FDA-approved treatment and a clinical trial (study treatment), visit www.LLS.org or contact an Information Specialist.

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REACH OUT TO OUR **INFORMATION SPECIALISTS**

The Leukemia & Lymphoma Society's (LLS) Information Specialists provide patients, families and healthcare professionals with the latest information on leukemia, lymphoma and myeloma.
Our team consists of master's level oncology social workers, nurses and health educators who are available by phone Monday through Friday, 9 am to 9 pm (ET).

Co-Pay Assistance
LLS's Co-Pay Assistance Program helps blood cancer patients cover the costs of private and public health insurance premiums, including Medicare and Medicaid, and co-pay obligations. Support for this program is based on the availability of funds by disease.
For more information, call 877.557.2672 or visit www.LLS.org/copay.

For a complete directory of our patient services programs, contact us at
800.955.4572 or **www.LLS.org**
(Callers may request a language interpreter.)

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For more information, please
contact our Information Specialists
800.955.4572 (Language interpreters
available upon request)
www.LLS.org

or:

National Office
3 International Drive, Suite 200
Rye Brook, NY 10573

Our Mission:
Cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families.

LLS is a nonprofit organization that relies on the generosity of individual, foundation and corporate contributions to advance its mission.

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