LEARNING that you have cancer can be overwhelming.

The goal of this book is to help you get the best cancer treatment. It explains which cancer tests and treatments are recommended by experts of chronic lymphocytic leukemia.

The National Comprehensive Cancer Network® (NCCN®) is a not-for-profit alliance of 27 leading cancer centers. Experts from NCCN have written treatment guidelines for doctors who treat leukemias. These treatment guidelines suggest what the best practice is for cancer care. The information in this patient book is based on the guidelines written for doctors.

This book focuses on the treatment of chronic lymphocytic leukemia. Key points of the book are summarized in the NCCN Quick Guide™ series on chronic lymphocytic leukemia. NCCN also offers patient resources on acute lymphoblastic leukemia, chronic myelogenous leukemia, multiple myeloma, and other cancer types. Visit NCCN.org/patients for the full library of patient books, summaries, and other resources.
These patient guidelines for cancer care are produced by the National Comprehensive Cancer Network® (NCCN®).

The mission of NCCN is to improve cancer care so people can live better lives. At the core of NCCN are the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). NCCN Guidelines® contain information to help health care workers plan the best cancer care. They list options for cancer care that are most likely to have the best results. The NCCN Guidelines for Patients® present the information from the NCCN Guidelines in an easy-to-learn format.

Panels of experts create the NCCN Guidelines. Most of the experts are from NCCN Member Institutions. Their areas of expertise are diverse. Many panels also include a patient advocate. Recommendations in the NCCN Guidelines are based on clinical trials and the experience of the panelists. The NCCN Guidelines are updated at least once a year. When funded, the patient books are updated to reflect the most recent version of the NCCN Guidelines for doctors.

For more information about the NCCN Guidelines, visit NCCN.org/clinical.asp.

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NCCN Foundation was founded by NCCN to raise funds for patient education based on the NCCN Guidelines. NCCN Foundation offers guidance to people with cancer and their caregivers at every step of their cancer journey. This is done by sharing key information from leading cancer experts. This information can be found in a library of NCCN Guidelines for Patients® and other patient education resources. NCCN Foundation is also committed to advancing cancer treatment by funding the nation’s promising doctors at the center of cancer research, education, and progress of cancer therapies.

For more information about NCCN Foundation, visit NCCNFoundation.org.
Endorsed by

The Leukemia & Lymphoma Society (LLS)
LLS is dedicated to developing better outcomes for blood cancer patients through research, education and patient services and is happy to have this comprehensive resource available to patients. www.LLS.org/InformationSpecialists

CLL Society Inc. (CLLS)
The CLL Society is a patient–centric, physician–curated nonprofit organization focused on patient education, support and research dedicated to addressing the unmet needs of the CLL (chronic lymphocytic leukemia) community. http://cllsociety.org
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Who should read this book?
The information in this book is about treatment of chronic lymphocytic leukemia. It is the most common type of leukemia in adults. It does not address treatment for small lymphocytic leukemia. Patients and those who support them—caregivers, family, and friends—may find this book helpful. It may help you discuss and decide with doctors what care is best.

Are the book chapters in a certain order?
Early chapters explain concepts that are repeated in later chapters. Starting with Part 1 may be helpful for many people. It explains what chronic lymphocytic leukemia is. Knowing more about this cancer may help you better understand its treatment.

Part 2 covers health tests and other care needed before starting treatment. It also shares factors that help doctors plan treatment.

Part 3 briefly describes all the types of treatment. Knowing what a treatment is will help you understand your options. Treatment options are presented in Part 4. Lastly, Part 5 shares questions for your doctors and directs you to online resources.

Help! What do the words mean?
In this book, many medical words are included. These are words you will likely hear from your treatment team. Most of these words may be new to you, and it may be a lot to learn.

Don’t be discouraged as you read. Keep reading and review the information. Feel free to ask your treatment team to explain a word or phrase that you don’t understand. Words that you may not know are defined in the text or in the Dictionary. Acronyms are also defined when first used and in the Glossary. One example is CLL for chronic lymphocytic leukemia.

Does this book include all options?
This book includes information for many situations. Your treatment team can help. They can point out what information applies to you. They can also give you more information. As you read through this book,
1 Chronic lymphocytic leukemia

8 Lymphocytes
9 CLL basics
11 First tests for CLL
13 Review
You’ve learned that you have or may have chronic lymphocytic leukemia. It’s common to feel shocked and confused. Part 1 reviews some basics about this leukemia that may help you learn about it and start to cope. These basics may also help you start planning for treatment.

**Lymphocytes**

There are many types of blood cells. Three main types are platelets, red blood cells, and white blood cells. Each type has a different job. Platelets help control bleeding. Red blood cells carry oxygen throughout the body. White blood cells help fight germs. They are a part of your body’s disease-fighting (immune) system.

Lymphocytes are a type of white blood cell and include NK (natural killer) cells, B-cells, and T-cells. NK cells release chemicals that kill diseased cells. B-cells make antibodies that mark germs for killing. T-cells alert your body that germs are present, kill diseased cells, and help B-cells. CLL is a cancer of these B-cells.

Most blood cells are made in bone marrow. See **Figure 1**. Bone marrow is the soft tissue in the center of most bones. Blood cells leave bone marrow and travel in blood throughout your body.

---

**Figure 1**

**Blood cells in bone marrow**

Most blood cells are first formed in the marrow of bones. Red blood cells, white blood cells, and platelets are the three main types of blood cells. Lymphocytes are a type of white blood cell. They help fight illness in your body.
There are many lymphocytes in bone marrow, blood, and your lymphatic system. Your lymphatic system consists of fluid, called lymph, and a network of tissues. Lymph travels in lymph vessels and passes through lymph nodes, which filter out germs and waste. Other organs of the lymphatic system include your thymus, spleen, and tonsils.

### CLL basics

Cancer is a disease of cells. Leukemias are cancers of white blood cells and start in bone marrow and blood. CLL (chronic lymphocytic leukemia) is one type of leukemia that starts in lymphocytes called B-cells. Since CLL is a cancer of blood cells, it can spread anywhere in the body that blood can go, including lymph nodes, bone marrow, and even solid organs.

CLL cells are found mostly within blood, bone marrow, and lymph nodes. SLL (small lymphocytic leukemia) is a cancer that also starts in B-cells but occurs mostly within the lymphatic system (lymph nodes). See Figure 2. CLL and SLL are thought to be the same cancer but differ in the fact that people with SLL do not have high numbers of white blood cells. Their treatment is very similar. The focus of this book is CLL. CLL occurs mostly in people who are middle aged or older.

### Figure 2

Lymph vessels and nodes

Lymph nodes and vessels are found throughout the body. A lymph node is a small group of special disease-fighting cells. Lymph nodes are connected to each other by a network of small tubes called lymph vessels.
Inside of cells are coded instructions for building new cells and controlling how cells behave. These instructions are called genes. Genes are a part of DNA (deoxyribonucleic acid), which is grouped together into bundles called chromosomes. See Figure 3. Changes (mutations) in genes cause normal B-cells to become cancer cells. Researchers are still trying to learn what causes genes to change and cause cancer.

Changes in genes cause cancer cells to grow more quickly and live longer than normal cells. Normal cells grow and then divide to form new cells when needed. They also die when old or damaged as shown in Figure 4.

In contrast, cancer cells make new cells that aren’t needed and don’t die quickly when old or damaged.

CLL can be a fast- or slow-growing cancer. Often, it grows slowly. If slow, you may not know you have CLL for years because you have no symptoms. Over time, CLL cells will crowd out healthy cells in bone marrow. A normal number of red blood cells and platelets will not be made. As a result, you may feel tired, lose weight, and get sick easily. CLL may also spread to your lymph nodes, liver, and spleen, and cause these organs to enlarge.

Figure 3
Genetic material in cells

Most human cells contain the “blueprint of life”—the plan by which our bodies are made and work. The plan is found inside of chromosomes, which are long strands of DNA that are tightly wrapped around proteins. Genes are small pieces of DNA that contain instructions for building new cells and controlling how cells behave. Humans have about 24,000 genes.
First tests for CLL

Your blood needs to be tested to confirm (diagnose) CLL. Often, CLL is suspected after a routine blood test that is part of your normal health care when it shows a high white blood cell or lymphocyte count. For a blood test, your doctor will insert a needle into your vein to remove a sample of blood. The needle may bruise your skin and you may feel dizzy from the blood draw. Your blood sample will then be sent to a lab where a pathologist will test it. A pathologist is a doctor who’s an expert in testing cells to find disease. The number of abnormal B-cells in your blood must be known for diagnosis. CLL requires the presence of at least 5,000 abnormal B-cells per microliter of blood (5 x 10^9/L). The B-cells have to be copies of the same “parent” cell. This is called monoclonality. See page 8 for more information on B-cells.

Figure 4
Normal cell growth vs. cancer cell growth

Normal cells increase in number when they are needed and die when old or damaged. In contrast, cancer cells quickly make new cells and live longer because of abnormal changes in genes.
For diagnosis, B-cells should also be tested for which proteins are in the cells’ surface (membrane). See Figure 5. This is called immunophenotyping (flow cytometry).

If there are fewer than 5,000 monoclonal B-cells, no enlarged lymph nodes, and no other signs of CLL, you may have MBL (monoclonal B-lymphocytosis). MBL is common, especially among older adults. It is not cancer and very few people with MBL develop CLL. The recommended care for MBL is observation. Observation or “watch and wait” is a period of testing to watch for changes in status. Some people won’t need treatment for years if at all.

A common test of cells is IHC (immunohistochemistry). This method involves applying a chemical marker to cells and looking at them with a microscope. Flow cytometry is a newer method by which some cell tests can be done. Flow cytometry can be used to count B-cells, confirm clonality, and do immunophenotyping. This method involves first adding a marker—a light-sensitive dye—to cells. Then, your blood will be passed through a flow cytometry machine. The machine measures surface proteins on thousands of cells. Flow cytometry is commonly used to diagnose CLL.

When being tested for CLL, mantle cell lymphoma needs to be ruled out. Mantle cell is a closely related type of blood cancer. This cancer has high levels of the protein called cyclin D1. There is too much cyclin D1 because of abnormal chromosomes in cells. To rule out mantle cell lymphoma, your blood may be tested with a cytospin machine for cyclin D1. Another test option is FISH (fluorescence in situ hybridization) to test for abnormal chromosomes.

Most often, flow cytometry on a blood sample can be used to diagnosis CLL. However, for some people, another method is needed. In these cases, a biopsy of your lymph nodes is advised.

A biopsy removes tissue samples to test for cancer. You will need anesthesia to numb the site. Then, part or all of one or more lymph nodes will be removed through a cut made in your skin. B-cells from the removed nodes will be tested with an IHC panel for the immunophenotype. The panel should include testing for CD3, CD5, CD10, CD20, CD23, and cyclin D1 proteins.

### Figure 5

**CD20 protein**

CLL cells have a common pattern of proteins in their membrane. This pattern includes the presence of CD5, CD19, and CD23 proteins, some CD20, and no CD10 proteins. Immunophenotyping is the process of identifying the proteins in cells’ membranes.
Review

- White blood cells are a part of your body’s immune system. Lymphocytes are a type of white blood cell and include NK cells, B-cells, and T-cells.

- Leukemias are cancers of white blood cells and start in bone marrow and blood. CLL is one type of leukemia that starts in B-cells.

- Your blood needs to be tested to diagnose CLL. To diagnose, doctors look for very high numbers of abnormal B-cells. They also look for proteins that are common and uncommon to CLL cells.

“

The key to managing fear is in making informed decisions. Stay positive, make a plan for yourself and go forward one step at a time.

- Ted

NCCN Guidelines for Patients®: Chronic Lymphocytic Leukemia, 2018
2

Treatment planning

15 Medical history
15 Physical exam
17 Blood tests
20 Imaging tests
21 Bone and marrow test
22 Heart tests
22 Fertility and pregnancy
23 Starting treatment
24 Review
Doctors plan treatment with many sources of information. One of these sources is tests of your health and the cancer. Part 2 describes who should receive which tests before treatment. Some of these tests are repeated during and after treatment. Besides tests, Part 2 describes other types of care that are important to receive before cancer treatment. Everyone does not need to start CLL treatment right away. Part 2 ends with explaining how doctors decide when treatment should be started.

Medical history

Your medical history includes any health events and medicines you’ve taken in your life. You will be asked about illnesses, injuries, health conditions, and more. Some health problems run in families. Thus, your doctor may also ask about the health of your blood relatives.

Some signs and symptoms of CLL are enlarged lymph nodes, tiredness, a feeling of fullness in your belly, and getting sick. CLL may also cause “B symptoms.” It’s important that your doctor knows if you have them. These symptoms include fevers, chills, night sweats, and weight loss without dieting.

A medical history is one of the tests needed for treatment planning. See Guide 1 on page 16 for a complete list of care that is recommended prior to treatment. Some types of care are for anyone with CLL while others may be useful for some people.

Physical exam

Doctors often give a physical exam along with taking a medical history. A physical exam is a exam of your body. Your doctor may listen to your lungs, heart, and intestines. With your permission, your doctor may also feel different parts of your body to see if organs are of normal size, are soft or hard, or cause pain when touched. For example, your doctor may feel your belly area (abdomen) to check for signs of disease. He or she will also measure the size of your liver and spleen if it can be felt.

Results of your medical history and physical exam will be used to rate your performance status. Performance status is your ability to do daily activities. It indicates a person’s general level of fitness. Along with labs, other studies, and your history, it is used by doctors to assess if you can undergo certain treatments.

Your medical records:

✓ Your doctors will order tests and schedule visits to talk about your care plan.

✓ It is helpful to keep track of your test results at all times. Ask your doctors questions about the results.
Guide 1. Care before treatment

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Blood tests

Blood tests are used to diagnose CLL as discussed in Part 1. For those people who need treatment, they may help doctors with treatment options. They are also used for at least three other reasons. First, blood tests can be used to know the outlook (prognosis) of a person with CLL; these tests are called prognostic markers. This means that they may help predict how fast the CLL may progress to needing treatment, or how long a treatment response may last. However, this is only an estimation from a study of groups of patients with similar prognostic markers; each person can be different. Prognosis is also likely to be different with the newer medications used for treatment.

Second, some blood tests are used to know the extent (stage) of cancer. How staging is related to starting treatment is discussed at the end of this chapter. Third, blood tests can help to find other diseases including those related to CLL. It’s important to treat all illnesses. Blood tests for CLL may include:

**Genetic tests**

**FISH test.** It is very common for CLL cells to have abnormal chromosomes. In CLL cells, chromosomes that commonly have defects include chromosomes 11, 12, 13, and 17. FISH is a test that is used to search for abnormal chromosomes and genes. FISH is sometimes used for diagnosis as described in Part 1 but also for prognosis. It can be done using either blood or bone marrow cells. It is a helpful test but not essential for treatment planning.

Missing (deleted) parts of chromosomes 11 or 17 are signs of a poor prognosis. A good prognosis is linked to deleted parts of chromosome 13, if it is the only abnormal chromosome. Trisomy is when there are three copies of a chromosome in a cell instead of the normal two. Trisomy 12 is linked to neither a poor nor a good prognosis.

**Karyotype.** A karyotype is a picture of the chromosomes in cells. It shows if there is a defect in the size, shape, and number of chromosomes. A blood or bone marrow sample can be used. Chemicals are added to the sample to start cell growth. For CLL, a chemical called CPG should be used.

A “complex karyotype” is linked to a poorer prognosis. A complex karyotype is when there are 3 or more unrelated defects in chromosomes that occur in more than one cell. The presence of a complex karyotype may affect your treatment options. Read Part 4 for more information.

**DNA sequencing.** DNA sequencing is a lab test of blood or marrow that is used to look for mutations in genes. A DNA sequencing test reveals the order of the chemicals that make up DNA. Certain gene mutations (abnormal changes) may be found with DNA sequencing. For CLL, DNA sequencing is used to test for mutations in the IGHV (immunoglobulin heavy-chain variable) region and TP53 genes. Immunoglobulins are Y-shaped proteins that help fight germs. In Part 1, they were described by their other name—antibodies. Normal antibodies are made of two heavy chain proteins and two light chain proteins. See Figure 6 on page 18. IGHV region genes in B-cells contain instructions for making the heavy chain protein. These genes may or may not be mutated in people with CLL. Prognosis is good if IGHV is mutated.

TP53 is the gene that makes a protein that signals for either the repair or destruction of damaged cells. Thus, it helps to prevent tumors from forming. DNA sequencing can be used to learn if this gene is mutated. If mutated, prognosis is poor.
**Cell protein tests**
Certain protein tests may be helpful in CLL, but not for every person. CD38, CD49d, and ZAP-70 levels, for example, can provide information on CLL prognosis. However, CD38, CD49d, and ZAP-70 levels are related to the IGHV mutation. If molecular analysis to test for IGHV is not an option, your doctor may test for CD38, CD49d, and ZAP-70. The IGHV testing is preferred as the protein levels are not as reliable.

**Complete blood count with differential**
A CBC (complete blood count) measures the number of blood cells in a blood sample. It includes numbers of white blood cells, red blood cells, and platelets. Your blood counts may be low or high because of cancer or another health problem. It is an essential test that gives a picture of your overall health.

There are several types of white blood cells in your body. A white cell differential counts the number of each type. It also checks if the counts are in balance with each other. Your doctor can learn from this test what the cause of an abnormal white blood count is. It is also used to stage the cancer and check if treatment is working.

**Comprehensive metabolic panel**
Chemicals in your blood come from your liver, bone, and other organs. A comprehensive metabolic panel often includes tests for up to 14 chemicals. The tests show if the level of chemicals are too low or high.

---

**Figure 6**
*Immunoglobulin (A.K.A antibody)*

Antibodies attach to germs so your immune system can find and destroy the germs. Normal antibodies are Y-shaped proteins made of two heavy chain proteins and two light chain proteins. Within CLL cells, the genes for making the heavy chain protein sometimes aren’t normal.
Abnormal levels can be caused by cancer or other health problems.

**Hepatitis B testing**
CLL and some of its treatments can cause the hepatitis B virus to become active again. Thus, tell your treatment team if you’ve ever been infected with hepatitis B. For others, ask your treatment team if you should get tested.

**Quantitative immunoglobulins**
There are three major types of antibodies in blood. They are IgG, IgA, and IgM. Your blood can be tested to measure the amount of each type of antibody. Testing will show if the level of any type of antibody is abnormal—too high or too low. See Figure 6.

Some people with CLL have low levels of antibodies before cancer treatment. They may be sick often. Testing of antibodies can help your doctors know if you need treatment to prevent or cure an infection.

**Haptoglobin**
Haptoglobin is a protein made by the liver. It attaches to free hemoglobin in blood to mark it for removal. Free hemoglobin is a protein with iron that was released from destroyed red blood cells.

Low amounts of haptoglobin can be a result of autoimmune hemolytic anemia. Autoimmune hemolytic anemia is when your body mistakes red blood cells for invaders and destroys them. Haptoglobin level is one of the tests needed to confirm autoimmune hemolytic anemia.

Autoimmune hemolytic anemia is common among people with CLL. Advanced CLL and some of its treatments can cause it. A cancer treatment called fludarabine should not be used if you have severe autoimmune hemolytic anemia.

**Reticulocyte count and direct Coombs test**
Low numbers of healthy red blood cells is called anemia. There are many causes of anemia. Two of the many causes are pure red cell aplasia and hemolysis. Pure red cell aplasia is when the early (precursor) cells that form into red blood cells are almost absent in bone marrow. Hemolysis is when red blood cells are being destroyed too early.

If you have anemia, you should be tested for these causes. Reticulocytes are precursor cells of mature red blood cells. Low numbers of reticulocytes is a sign of pure red cell aplasia, and high numbers indicate hemolysis. The other test is a direct Coombs test. This test can detect if antibodies are stuck to and killing red blood cells.

**Beta-2 microglobulin**
Beta-2 microglobulin is a small protein made by many types of cells, including CLL cells. It is measured with a blood chemistry test. High levels of this protein may be a sign of CLL that is harder to treat.

**LDH**
LDH is a protein that is in most cells. It gets into your blood when a cell is damaged. Thus, a high level of lactate dehydrogenase is a sign of cell damage. High levels can be caused by cancer or other health problems. If related to cancer, high levels may be a sign that treatment may be needed now or soon.

**Uric acid**
Some people with CLL are at risk for tumor lysis syndrome. This syndrome can be life threatening. It occurs when the waste released by dead cells is not quickly cleared out of your body. This results in kidney damage and severe blood electrolyte disturbances.
Tumor lysis syndrome can occur among people with CLL who are undergoing strong cancer treatments. The cancer treatment kills many cancer cells and results in too much waste. See page 49 for more information on tumor lysis syndrome.

Your doctors may want to know your uric acid levels before starting treatment. You may be given certain medications that can help prevent tumor lysis syndrome. Also, drinking plenty of water throughout chemotherapy can help. Ask your treatment team for more information.

**Imaging tests**

Imaging tests make pictures (images) of the inside of your body. They can show where cancer is. Depending on the test, you may need to stop taking some medicines and stop eating and drinking for a few hours before the scan. If you are nervous, you may be given a drug, called a sedative, to help you relax.

Imaging machines are large. You will likely be lying down during testing. At least part of your body will be in the machine. See Figure 7 for a type of imaging machine called a CT (computed tomography) scan.

After the test, you will likely be able to resume your activities right away. If you took a sedative, you will have a waiting period. You may not learn of the results for a few days since a radiologist needs to see the pictures. A radiologist is a doctor who’s an expert in reading the images.

After the test, you will likely be able to resume your activities right away. If you took a sedative, you will have a waiting period. You may not learn of the results for a few days since a radiologist needs to see the pictures. A radiologist is a doctor who’s an expert in reading the images.

**CT scan**

A CT scan may be needed before starting and during treatment. CT takes many pictures of a body part from different angles using x-rays. A computer combines the x-rays to make detailed pictures.

A contrast dye is used for CT. It makes the pictures clearer. The dye will be injected into a vein in your hand or arm. You will also be given a liquid contrast to drink.

**Figure 7**

CT machine

Pictures of the insides of your body can be made with an imaging test. During the scan, you will lie on a table that will move into the tunnel of the imaging machine. The pictures will be viewed by a doctor who will look for signs of cancer.
The contrast may cause you to feel flushed or get hives. Rarely, serious allergic reactions occur. Tell your doctor and the technicians if you have had bad reactions to contrast. Also, tell them if you get nervous when in small spaces. You may be given a sedative to help you relax.

CT is needed if you have symptoms suggesting your lymph nodes are large. If needed, a CT of your chest, belly area, and between your hip bones is advised. CT scans received during treatment can help your doctors know if treatment is working.

**PET/CT scan**
CT is sometimes done along with another imaging test called PET (positron emission tomography). For PET, a sugar radiotracer will be injected into your body. The radiotracer is detected with a special camera. Cancer cells appear brighter than normal cells because they use sugar (glucose) more quickly.

PET/CT is often not useful for CLL. If given, it is used to help direct a needle into a lymph node for a biopsy. Your lymph nodes may be tested if your doctor thinks that CLL is turning into a fast-growing cancer like diffuse large B-cell lymphoma. PET/CT is an essential test for this cancer.

**Bone and marrow test**
A bone marrow biopsy removes a sample of bone and soft bone marrow. A bone marrow aspiration removes a small amount of liquid bone marrow. These tests aren’t needed to diagnose CLL. However, your doctor may order these tests to learn what’s causing low numbers of blood cells.

Often, these tests are done at the same time on the back of hip bone. You may receive a light sedative before the test. You will likely lie on your side as shown in Figure 8. Your doctor will clean your skin then give local anesthesia to numb the site. Once numb, a hollow needle will be inserted into your skin and then pushed into the bone to remove the liquid bone marrow with a syringe. Then, a wider needle will be inserted into the bone and rotated to remove bone and soft marrow. These biopsies may cause bone pain and can bruise your skin for a few days. The samples will be sent to a lab for testing.
Heart tests

Some cancer treatments can damage your heart. Thus, your doctor may test how well your heart works to plan treatment. If it isn’t working well, you may receive other treatment.

An echocardiogram is an imaging test of your heart. It uses sound waves (ultrasound) to make pictures. During this test, you will be lying down. Small patches will be placed on your chest to track your heartbeat. Next, a probe with gel on its tip will be slid across part of your bare chest. A picture of your beating heart will be seen at once on a screen. The pictures will be recorded for future viewing.

A MUGA (multi-gated acquisition) scan measures how well your heart is pumping blood. For this test, patches will be placed on your chest to track your heartbeat. Also, a radiotracer will be injected into your vein. Pictures of your heart will be taken with a special camera that can detect the radiation released by the tracer.

Sperm banking
Men who want to father children after cancer treatment can use sperm banking. Sperm banking stores semen for later use. This is done by freezing semen with sperm in liquid nitrogen. Talk to your treatment team about the costs of and how well sperm banking works.

Egg freezing and more
Like sperm banking, a woman’s eggs can be removed, frozen, and stored for later use. Your frozen eggs can be fertilized with sperm beforehand. Also, a part of your ovary that contains eggs can be frozen and stored.

Pregnancy test
Some cancer treatments can harm an unborn baby. Get a pregnancy test before treatment if you may be pregnant now. Your treatment options will depend on the results. During treatment, take steps to avoid getting pregnant. Your doctors can tell you which birth control methods are best to use while on treatment.

Fertility and pregnancy

Some cancer treatments can limit your ability to have a baby. If you want the choice of having babies after treatment or are unsure, tell your doctors. It may also help to talk with a fertility specialist before you begin cancer treatment. A fertility specialist is an expert in helping people have babies. The fertility specialist can discuss with you how to have a baby after treatment. Some methods of fertility preservation are discussed next. If you are a woman of childbearing age, important information on pregnancy is also addressed.

Helpful tips:

- Keep a list of contact information of all of your health care providers.
- Ask a caregiver to help you plan your appointments.
- Use a calendar or day planner to keep track of your appointments.
**Starting treatment**

Part of treatment planning involves deciding when to start treatment. Not all people with CLL need to start treatment right away. Starting treatment is based on symptoms of CLL, test results, and the cancer stage. The cancer stage is a rating by your doctors that suggests what the prognosis of the cancer is.

The Rai staging system will help your doctor decide whether to start treatment or not. This system consists of five cancer stages. The cancer stages are defined by the results of your physical exam and blood tests. The five stages are:

- **Stage 0** is defined by normal test results except for a high number of lymphocytes in blood. The likelihood of the cancer getting worse is low.

- **Stage I** is defined as a high number of lymphocytes in blood and enlarged lymph nodes. The likelihood of the cancer getting worse is intermediate.

- **Stage II** is defined by an enlarged liver, spleen, or both. The likelihood of the cancer getting worse is intermediate.

- **Stage III** is defined by a low hemoglobin level. The likelihood of the cancer getting worse is high.

- **Stage IV** is defined by a low platelet count. The likelihood of the cancer getting worse is high.

You may hear of the Binet staging system. It is another system used to stage CLL. It has three stages labeled A, B, and C. The stages are based on your physical exam and blood tests. The Binet system may be helpful for prognosis but isn’t used in this book to decide starting treatment.

If you have Rai stage 0, I, and II CLL, treatment may not be needed now. You should be further assessed to learn if treatment is needed.

Signs to start treatment include:

- Symptoms of active CLL, such as drenching night sweats
- Severe fatigue
- Fever without proof of infection
- Unplanned weight loss

If these signs are not present, observation is advised. Treatment can be started when any of the listed signs appear or the cancer advances to stage III or IV.

Most people with stage III or IV CLL need to be treated, even when newly diagnosed. In some cases, observation may be an option if your blood cell counts aren’t too low and don’t drop more. Treatment is advised if the cancer is stage III and IV and your blood cell counts are falling.
Review

- Tell your doctor if you have recently had fevers, night sweats, and weight loss without dieting. These can be symptoms of CLL.

- Your doctor will examine your body for signs of disease. He or she will check the size of your liver and spleen. Your doctor will also rate your ability to do everyday activities.

- Blood tests can be done to assess the prognosis of CLL and for other health conditions.

- Imaging tests allow your doctors to see inside your body without cutting into it. CT and PET/CT scans may be useful in certain cases.

- A bone marrow biopsy removes a piece of bone and marrow to test for cancer cells. An aspiration removes liquid marrow. These tests may be helpful before starting treatment.

- You may undergo heart tests to see if you are healthy enough to have certain cancer treatments.

- Talk to a fertility specialist to learn about ways to have babies after cancer treatment. If you may be pregnant now, get a pregnancy test since some cancer treatments can harm unborn babies.

- You may not need to start treatment for CLL right away. Your doctors will decide whether to advise starting treatment based on the signs and symptoms of CLL, test results, and the cancer stage.
# Overview of cancer treatments

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NCCN Guidelines for Patients®: Chronic Lymphocytic Leukemia, 2018
In Part 3, the main treatment types that are recommended by NCCN experts for CLL are briefly described. These treatments are for people who have or will be starting treatment. Knowing what a treatment is will help you understand your treatment options listed in Part 4. There is more than one treatment for CLL. Not every person with CLL will receive every treatment described in this chapter.

Clinical trials

New tests and treatments aren’t offered to the public as soon as they’re made. They first need to be studied. A clinical trial is a type of research that studies a test or treatment. Clinical trials are the preferred treatment option of NCCN experts for CLL.

Clinical trials study how safe and helpful tests and treatments are. When found to be safe and helpful, they may become tomorrow’s standard of care. Because of clinical trials, the tests and treatments in this book are now widely used to help people with CLL. Future tests and treatments that may have better results than today’s treatments will depend on clinical trials.

New tests and treatments go through a series of clinical trials to make sure they’re safe and work. Without clinical trials, there is no way to know if a test or treatment is safe or helpful. Clinical trials have four phases. Some examples of the four phases for treatment are:

- **Phase I trials** – aim to find the best dose of a new drug with the fewest side effects.

- **Phase II trials** – assess if a drug works to treat a specific type of cancer.

- **Phase III trials** – compare a new drug to the standard treatment.

- **Phase IV trials** – test new drugs approved by the U.S. FDA (Food and Drug Administration) in many patients with different types of cancer.

Joining a clinical trial has benefits. First, you’ll have access to the most current cancer care. Second, you will receive the best management of care. Third, the results of your treatment—both good and bad—will be carefully tracked. Fourth, you may help other people who will have cancer in the future.

Clinical trials have risks, too. Like any test or treatment, there may be side effects. Side effects are unhealthy or unpleasant physical or emotional responses to treatment. Also, new tests or treatments may not help. Another downside may be that paperwork or more trips to the hospital are needed.

To join a clinical trial, you must meet the conditions of the study. Patients in a clinical trial are often alike in terms of their cancer and general health. This is to know that any progress is because of the treatment and not because of differences between patients. Likewise, some clinical trials are only open to people who have not started treatment while others are.

To join, you’ll need to review and sign a paper called an informed consent form. This form describes the study in detail. The study’s risks and benefits should be described and may include others than those listed above.

Ask your treatment team if there is an open clinical trial that you can join. There may be clinical trials where you’re getting treatment or at other treatment centers nearby. You can also find clinical trials through the websites listed in Part 5.
Chemotherapy

Chemotherapy, or “chemo,” includes drugs that disrupt the life cycle of cancer cells so they can’t increase in number. Some chemotherapy drugs kill cancer cells by damaging their DNA or by disrupting the making of DNA. Other drugs interfere with cell parts that are needed for making new cells. Thus, no new cells are made to replace dying cells. Chemotherapy is often used to treat CLL.

Many chemotherapy drugs work when cells are in an active growth phase. During the active growth phase, cells grow and divide to form a new cell. Chemotherapy drugs that disrupt the growth phase work well for cancer cells that are growing and dividing quickly. Other chemotherapy drugs work whether cells are in a growth or resting phase. Chemotherapy can kill both cancer and normal cells.

Most chemotherapy drugs for CLL are liquids that are slowly injected into a vein. Some are made as pills that can be swallowed. By any method, the drugs travel in your bloodstream to treat cancer throughout your body. Doctors use the term “systemic” when talking about a cancer treatment for the whole body. Chemotherapy and other drugs used to treat CLL are listed in Guide 2 on the next page.

Chemotherapy is given in cycles of treatment days followed by days of rest. This allows the body to recover before the next cycle. Cycles vary in length depending on which drugs are used. Often, one total cycle is 4 weeks long.

Chemotherapy may consist of one or more drugs. When only one drug is used, it is called a single agent. However, not all drugs work the same way, so often more than one drug is used. A combination regimen is the use of two or more chemotherapy drugs.

Part 4 is a guide that explains who should receive which treatments. You will learn which regimens may be part of your treatment. Chemotherapy is sometimes given in high doses and followed by a stem cell transplant. Stem cell transplants are described later in this chapter.

Side effects of chemotherapy

Side effects of chemotherapy differ between people. Some people have many side effects. Others have few. Some side effects can be very serious while others can be unpleasant but not serious. Most side effects appear shortly after treatment starts and will stop after treatment. However, other side effects are long-term or may appear years later.

Side effects of chemotherapy depend on many factors. These factors include the drug type, amount taken, length of treatment, and the person. In general, most side effects are caused by the death of fast-growing cells. These cells are found in the blood, gut, hair follicles, and mouth. Thus, common side effects of chemotherapy include low blood cell counts, not feeling hungry, nausea, vomiting, diarrhea, hair loss, and mouth sores. Long-term side effects of chemotherapy for CLL include increased risk for getting infections.

Not all side effects of chemotherapy are listed here. Please ask your treatment team for a complete list of common and rare side effects. If a side effect bothers you, tell your treatment team. There may be ways to help you feel better. There are also ways to prevent some side effects.
Guide 2. Drug treatment for CLL

<table>
<thead>
<tr>
<th>Generic name</th>
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<td>Bendamustine hydrochloride</td>
<td>Treanda®, Bendeka™</td>
<td>Chemotherapy</td>
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<td>Fludarabine phosphate</td>
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<td>Imbruvica®</td>
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<td>Zydelig®</td>
<td>Targeted therapy</td>
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<tr>
<td>Lenalidomide</td>
<td>Revlimid®</td>
<td>Immunotherapy</td>
</tr>
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<td>Steroid</td>
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<td>Vincristine sulfate</td>
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<td>Chemotherapy</td>
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Steroids

Steroids are a type of drug that is often used to relieve inflammation. Steroids can also have anti-cancer effects. Methylprednisolone is a corticosteroid used to treat CLL. Read Part 4 for more information on when it’s used.

Methylprednisolone is given in high doses along with rituximab. Rituximab is described in the Targeted therapy section in this chapter. Methylprednisolone can either be injected into your vein or swallowed in pill form. It is often taken for a few days during a 1-month cycle.

Prednisone is another steroid that is used to treat CLL. It is given along with some chemotherapy regimens. Prednisone is made in pill form and is taken once a day with food.

Most side effects of steroids fade away once the drugs are stopped. Common side effects include feeling hungry, trouble sleeping, slow wound healing, upset stomach, and swelling in the ankles, feet, and hands. Methylprednisolone with rituximab increases the likelihood of getting infections.

Immunomodulators

The immune system is your body’s natural defense against illness. Immunomodulators are drugs that modify different parts of the immune system. Lenalidomide is an immunomodulator used to treat CLL.

Lenalidomide is made in pill form. It is given in cycles of treatment days followed by days of rest. A cycle may consist of 3 weeks of treatment and 1 week of rest. It may also be given for 4 straight weeks. Cycles may repeat until the cancer grows or side effects become severe.

Lenalidomide treats cancer in more than one way. As an immunomodulator, it boosts the immune system. It also helps stop cancer cells from increasing in number. Third, it also works like a type of targeted therapy called angiogenesis inhibitors. These drugs stop the growth of new blood vessels that would provide food (nutrients) to the cancer.

Common side effects include low blood counts, diarrhea, itching, rash, and fatigue. Serious but less common side effects include blood clots, bleeding disorders, loss of vision, and skin cancer. Ask your treatment team for a full list of side effects.
Targeted therapy

Targeted therapy is a class of drugs that stops the action of molecules that help cancer cells grow. It is less likely to harm normal cells than chemotherapy. There are multiple targeted therapies that are used to treat CLL. They include monoclonal antibodies and kinase inhibitors.

Monoclonal antibodies are man-made antibodies that attach to proteins on cancer cells. The monoclonal antibodies used to treat CLL attach to antigens. When antibodies are attached to antigens on a cell, the cell is marked to be destroyed by your immune system.

Kinases are molecules that move chemicals, called phosphates, from one molecule to another. Kinase inhibitors stop the phosphates from being moved. Kinase inhibitors often block growth signals within cancer cells. This reduces the number of new cancer cells being made.

Next, the targeted therapies for CLL are briefly described. Some side effects are listed. Ask your treatment team for a full list of common and rare side effects. In Part 4, information on who should receive these drugs is provided.

Alemtuzumab

Alemtuzumab is a monoclonal antibody that attaches to a molecule called CD52. CD52 is found on CLL cells, healthy B-cells and T-cells, as well as other cells. Alemtuzumab is used alone and sometimes with other medicines to treat CLL.

Alemtuzumab is a liquid that will be slowly injected into your vein. It may take up to two hours to get the full dose. Alemtuzumab can also be given as an injection under the skin. Alemtuzumab is often given three times a week for 12 weeks.

Common side effects include an allergic reaction when receiving the medicine. Also, you may feel nausea, vomit, get diarrhea, and have trouble sleeping. Blood counts are often low when taking this medicine. Taking alemtuzumab will increase your chances of getting a cytomegalovirus or other infection.

Ibrutinib

Ibrutinib is a kinase inhibitor. It stops a kinase called BTK (Bruton’s tyrosine kinase). This kinase is found inside of CLL cells and normal B-cells.

Ibrutinib is usually taken without other cancer medicines to treat CLL. It is made in pill form and taken once a day around the same time. Your doctor will tell you how many pills you need for your dose.

Common side effects of ibrutinib include diarrhea, tiredness, muscle and bone pain, bruising, nausea, upper respiratory tract infection, and rash. There may be a short-lived increase in lymphocytes when first taking ibrutinib. Serious but uncommon side effects include bleeding, severe infections, heart and kidney problems, and other cancers.

Idelalisib

Idelalisib is a kinase inhibitor. It stops a kinase called PI3K (phosphoinositide 3-kinase delta). This kinase is found inside of CLL cells and normal B-cells.

Idelalisib is used alone or sometimes with rituximab to treat CLL. It is made in pill form and is taken twice a day. Your doctor will tell you how many pills you need for your dose.

Common side effects of idelalisib include diarrhea, fever, fatigue, nausea, cough, lung infection, belly pain, chills, and rash. White blood counts are often low when taking this medicine. However, there may be a short-lived increase in lymphocytes when first taking idelalisib.
Serious but uncommon side effects include liver and lung problems, skin problems, severe diarrhea, and holes in your gut.

**Venetoclax**  
Venetoclax is a small molecule inhibitor that targets the BCL-2 protein. This type of targeted therapy stops a function within the cell that helps it survive.

Venetoclax is used alone or sometimes with rituximab to treat CLL. It is recommended for CLL that responds to treatment but comes back (relapsed), or the first treatment doesn’t work (refractory). It is made in pill form and is taken once a day.

Common side effects of venetoclax are low blood cells counts, diarrhea, nausea, upper respiratory tract infection, and tiredness. Venetoclax also increases your chances for tumor lysis syndrome. Ask your treatment team for a full list of side effects.

**Obinutuzumab**  
Obinutuzumab attaches to a molecule on CLL cells called CD20. See Figure 9. It works by marking cells for destruction but it may directly kill the cells, too. It is used alone and sometimes with chemotherapy to treat CLL.

Obinutuzumab is a liquid that will be slowly injected into your vein. It takes a few hours to get the full dose. Obinutuzumab is given on some days during six 28-day treatment cycles.

You may have an allergic reaction while receiving obinutuzumab. Tumor lysis syndrome, infections, diarrhea, nausea, fatigue, and rash. Hepatitis B can be reactivated while taking obinutuzumab.

**Ofatumumab**  
Ofatumumab is another monoclonal antibody that attaches to CD20. However, it attaches to a different part of CD20. It is used alone and sometimes with chemotherapy to treat CLL.

Ofatumumab is a liquid that will be slowly injected into your vein. It takes about 6 hours to receive the first dose. Other doses may be given in less time. Ofatumumab is often given once a week for 8 weeks. Then it’s restarted after a 4- or 5-week break. After the break, ofatumumab is often received once a month for four months.

You may have an allergic reaction while receiving ofatumumab. Other common side effects include low blood cell counts, infections, diarrhea, nausea, fatigue, and rash. Hepatitis B can be reactivated while taking ofatumumab.

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**Figure 9**  
Anti-CD20 monoclonal antibody

Anti-CD20 monoclonal antibodies attach to CLL cells to mark them for destruction by your immune system.

![Anti-CD20 monoclonal antibody](https://commons.wikimedia.org/wiki/File:Rituxima_Binding_to_CD20_on_a_B_Cell_Surface_(6830897205).jpg) available at commons.wikimedia.org/wiki/File:Rituxima_Binding_to_CD20_on_a_B_Cell_Surface_(6830897205).jpg under a Creative Commons Attribution 2.0 Generic license
**Rituximab**

Like obinutuzumab and ofatumumab, rituximab also attaches to CD20. It works by marking cells for destruction but it may directly kill the cells, too. It is sometimes used alone, with chemotherapy, or with another targeted therapy to treat CLL.

Rituximab is a liquid that will be slowly injected into your vein. It often takes a few hours to receive the full dose. How often you will receive rituximab depends on what other cancer medicines you are receiving.

You may have an allergic reaction while receiving rituximab. Other common side effects are chills, infections, body aches, tiredness, and low blood cell counts. Rituximab also increases your chances for tumor lysis syndrome, heart problems, and blockage and holes in your gut.

**Stem cell transplant**

Hematopoetic stem cells are cells that develop into mature blood cells. Stem cells and mature blood cells are made in bone marrow. The goal of a stem cell transplant is to cure cancer by replacing unhealthy blood stem cells with healthy ones that will attack cancer cells. This is done by suppressing the bone marrow and cancer with chemotherapy then transplanting healthy blood stem cells. The healthy blood stem cells will grow, form new marrow and blood cells, and attack remaining cancer cells. Using stem cells from a donor is called an allogeneic stem cell transplant. Besides a new immune system, another benefit of this transplant is the GVL (graft-versus-leukemia) effect. The GVL effect is an attack on cancer cells by the transplanted stem cells.

Allogeneic stem cell transplant is sometimes used to treat CLL. It is an option for some people after drug treatment has been received. The steps of treatment with allogeneic stem cell transplant are described next.

**HLA typing**

Special testing must be done to find the right donor for you. The donor and your tissue type must be a near-perfect match for this treatment to work. The test used to check tissue type is called HLA (human leukocyte antigen) typing. A blood sample is needed to perform the test.

**Conditioning chemotherapy**

Before the transplant, you will receive chemotherapy. The chemotherapy will suppress your immune system, allowing the donor cells to grow. The high-dose chemotherapy also destroys normal cells in the bone marrow. This greatly weakens your immune system so that your body doesn’t kill the transplanted stem cells. Not every person can tolerate the high-dose chemotherapy before the transplant. Side effects of chemotherapy are described earlier in this chapter.

**Transplanting stem cells**

After chemotherapy, you will receive the healthy stem cells through a transfusion. A transfusion is a slow injection of blood products through a central line into a large vein. A central line (or CVC, central venous catheter) is a thin tube. The tube will be inserted into your skin through one cut and into your vein through a second cut. Local anesthesia will be used. This process can take several hours to complete.

The transplanted stem cells will travel to your bone marrow and grow. New, healthy blood cells will form. This is called engraftment. It usually takes about 2 to 4 weeks.

Until then, you will have little or no immune defense. You may need to stay in a very clean room at the hospital. You may be given an antibiotic to prevent or treat infection. You may also be given a blood transfusion to prevent bleeding and to treat anemia. While waiting for the cells to engraft, you will likely feel tired and weak.
Complementary and alternative medicine

CAM (complementary and alternative medicine) is a group of treatments sometimes used by people with cancer. Many CAMs are being studied to see if they are truly helpful.

- Complementary medicines are meant to be used alongside standard therapies, most often for relaxation, improving your health, or to prevent or reduce side effects.

- Alternative medicine is treatment or techniques that are used instead of standard treatments such as chemotherapy or radiation. Some are sold as cures even though they haven’t been proven to work in clinical trials.

Many cancer centers or local hospitals have complementary therapy programs that offer acupuncture, yoga, and other types of therapy.

It’s important to tell your treatment team if you are using any complementary medicine, especially supplements, vitamins, or herbs. Some of these can interfere with your cancer treatment. For example, some supplements or herbs can increase or decrease levels of chemotherapy or targeted therapy drugs in your body. This may cause more side effects or make the treatment not work as well. For more information about CAM, ask your doctor and visit the websites in Part 5.
Review

- Clinical trials give people access to new tests and treatments that otherwise can’t usually be received. These new tests and treatments may, in time, be approved by the FDA.

- Chemotherapy stops the life cycle of cancer cells so they can’t increase in number.

- Some steroids have anti-cancer effects and may be used with chemotherapy.

- Lenalidomide treats CLL by modifying your immune system and by other means.

- Some targeted therapies for CLL mark the cancer cells for destruction by your immune system. Other targeted therapies stop the cancer cells from receiving signals to grow.

- A stem cell transplant destroys bone marrow then replaces it by adding healthy stem cells into your body.

“It is essential to have a doctor that you trust implicitly, and who knows that you are the ultimate decision-maker in your treatment regimen. If you can’t advocate for yourself, ask a family member or friend for help.

- Dixie
4 Treatment guide

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Clinical trials are the preferred treatment option of CLL experts for people with CLL. If you are unable or don’t want to join a clinical trial, Part 4 lists other treatment options for you. The first sections in Part 4 address treatment for CLL, and the last section addresses supportive care.

The information in Part 4 is taken from the treatment guidelines written by NCCN experts of CLL. These treatment guidelines list options for people with CLL in general. Thus, your doctors may suggest other treatment for you based on your health and personal wishes. Fully discuss your treatment options with your doctor.

Treatment options for CLL

There are multiple treatment options for CLL. Treatment options that are best for you depend on features of the cancer and sometimes your age and health status. Thus, treatment options in Part 4 are grouped by these factors.

The cancer feature that is very important for CLL treatment is whether there are missing parts of chromosome 17 or TP53 gene mutation (see page 17 for more details). The standard of care differs based on this cancer feature. The word “del(17p)” is how doctors refer to missing parts of chromosome 17. Abnormal TP53 genes have been seen in patients that don’t have del(17p). If unsure, ask your doctor if tests showed that you have del(17p) and/or TP53 mutation.

The treatment options start with a first-line treatment. First-line treatment is the first treatment offered to treat the cancer. When that treatment is finished, your doctor will check if the cancer is responding to the treatment, assessing if it is working or not.

Before starting treatment again, your doctor may want to test the cancer again. Features of cancer can change over time, so re-testing may be needed if some time has passed. Testing of chromosomes 11, 12, 13, and 17 with FISH is recommended. Also, TP53 and karyotype will be assessed. Your doctor may advise you to get an imaging test. If del(17p) is found, you will refer to Guides 9 and 10.

For some individuals, the next treatment is maintenance therapy. Your doctor may also prescribe maintenance therapy to maintain the good results of your first-line treatment. If the treatment isn’t working or the cancer returns after treatment, other options are considered to treat refractory or relapsed CLL. After these treatment options, other treatment may be considered and include a clinical trial or an allogeneic SCT in some cases.

Treatment options by age, fitness, and health

When doctors plan treatment for CLL, one of the first steps is to exclude any treatment that is likely to be life-threatening. Chemotherapy is sometimes part of the standard of care for CLL without del(17p). However, some types are more likely to cause life-threatening infections to some people. Your doctor will decide your risk based on your physical ability fitness and health.

Treatment options in Part 4 are grouped by your fitness and health. The first section focuses on people who are frail and sick and should avoid purine analogs. The list of treatment options are least likely to cause life-threatening infections. See Guide 3 on page 38 to learn which options are recommended by NCCN experts for this group.
The second section is for younger and fairly healthy people. It starts on page 40. This section is for people who are younger than 65 years of age and are fairly healthy besides having cancer. The standard of care includes a purine analog.

The next section is for people who are older or quite sick. It is for those who are: 1) 65 years of age and older; or 2) younger than 65 years but have serious health problems in addition to cancer. Some of the treatment options for this group include a purine analog.

On page 45 you will read about Richter’s transformation (including DLBCL [diffuse large B-cell lymphoma] and Hodgkin lymphoma) and CLL with progression. Some people with CLL can develop these cancers or the cancer itself can progress. The testing before treatment is similar to CLL workup but treatment options may differ for each cancer type.

Lastly, you will learn about supportive care options. Supportive care is treatment given to relieve the health problems caused by cancer and side effects of cancer treatment. Managing symptoms and side effects with supportive care is important for your quality of life and treatment outcome.
Treatment for CLL without del(17p) or TP53 mutation

Guide 3. Treatments excluding purine analogs

Frail and sick

<table>
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<th>Treatment options (best options listed first)</th>
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<tr>
<td>• Ibrutinib</td>
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<tr>
<td>• Ofatumumab + chlorambucil</td>
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<tr>
<td>• Rituximab + chlorambucil</td>
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<tr>
<td>• Obinutuzumab</td>
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<tr>
<td>• HDMP (high-dose methylprednisolone) + rituximab</td>
</tr>
<tr>
<td>• Rituximab</td>
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<tr>
<td>• Chlorambucil</td>
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Guide 3 lists first-time treatment options for older or younger sick people who have CLL that isn’t missing parts of chromosome 17 or has a TP53 mutation. The treatment options are listed in order of preference of NCCN experts. Your doctors may think you cannot withstand purine analogs. This type of chemotherapy increases the likelihood of serious infections. Purine-analogs include fludarabine, cladribine, and pentostatin.

Purine analogs can reduce normal white blood cells to very low levels. It can take years for some white blood cells to increase to normal levels. If you take purine analogs, you may increase your chances for getting life-threatening infections.

Compared to purine analogs, there are safer treatment options if you are physically frail and overall quite sick. Some of these treatments consist of both targeted therapy and chemotherapy. They include obinutuzumab with chlorambucil, ofatumumab with chlorambucil, and rituximab with chlorambucil. The second drug listed in Guide 3 is ibrutinib. It is a targeted drug and is included based on good results in well-designed clinical trials.

Other options include taking a pulse corticosteroid with rituximab corticosteroids given in high doses over 3 to 5 days. One combination in Guide 3 includes HDMP and rituximab. Obinutuzumab, rituximab, and chlorambucil may each be used as a single agent to treat CLL. Chlorambucil by itself is the least preferred option.

After first-line treatment, your doctor may consider maintenance therapy with lenalidomide if you are at high risk for the disease to relapse (come back). Your doctor will test for MRD after first-line treatment. MRD is when a very small amount of leukemia cells remains in your body after a course of treatment. With MRD, the amount of leukemia cells left is too small to be seen with a microscope. Thus, further treatment may be given.
Guide 4 lists treatment options for if the CLL responds but comes back (relapsed), or if the first treatment doesn't work (refractory). This is treatment for relapsed or refractory disease for patients who are frail or sick, whether young or older. Before starting treatment, your doctor may want to test the cancer again. Features of cancer can change over time, so re-testing of the chromosomes in the cancer cells is advised. These tests include FISH, karyotype, and TP53 mutation status. The results are helpful in deciding on the next best treatment.

If the features haven't changed, ibrutinib alone and idelalisib with rituximab are preferred options. They are preferred due to good results measured in well-designed clinical trials. There are other drug options in Guide 4 that are listed in order of preference of NCCN experts.

If you have a complete or partial response to treatment for refractory or relapsed disease, your doctor may consider a second maintenance therapy with lenalidomide or ofatumumab. Your doctor will test for MRD and decide on your next steps based on those results. MRD is when a very small amount of leukemia cells remains in your body after a course of treatment. With MRD, the amount of leukemia cells left is too small to be seen with a microscope. It is helpful to ask your doctor to explain any further treatment options you may have.

Richter’s transformation is when CLL becomes a lymphoma such as DLBCL or Hodgkin lymphoma. CLL can also transform at a cellular level to another type of B-cell cancer called B-cell prolymphocytic leukemia. These cancer types can be aggressive and may follow a different treatment plan. See Guides 12 and 13.

### Guide 4. Treatments if prior treatment fails

#### Frail and sick

<table>
<thead>
<tr>
<th>Treatment options (best options listed first)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ibrutinib</td>
</tr>
<tr>
<td>• Idelalisib + rituximab</td>
</tr>
<tr>
<td>• Venetoclax ± rituximab</td>
</tr>
<tr>
<td>• Idelalisib</td>
</tr>
<tr>
<td>• Reduced-dose FCR (fludarabine, cyclophosphamide, rituximab)</td>
</tr>
<tr>
<td>• Reduced-dose PCR (pentostatin, cyclophosphamide, rituximab)</td>
</tr>
<tr>
<td>• HDMP + rituximab</td>
</tr>
<tr>
<td>• Rituximab + chlorambucil</td>
</tr>
<tr>
<td>• Ofatumumab</td>
</tr>
<tr>
<td>• Obinutuzumab</td>
</tr>
<tr>
<td>• Lenalidomide ± rituximab</td>
</tr>
<tr>
<td>• Alemtuzumab ± rituximab</td>
</tr>
<tr>
<td>• Dose-dense rituximab</td>
</tr>
<tr>
<td>• Bendamustine + rituximab ± ibrutinib</td>
</tr>
<tr>
<td>• Bendamustine + rituximab ± idelalisib</td>
</tr>
</tbody>
</table>
Guide 5 lists first-time treatment options for younger, healthy people with CLL that isn’t missing parts of chromosome 17 or has a TP53 mutation. FCR is the standard of care. FCR has been tested in well-designed clinical trials and has had good results for younger people with CLL. Other options include those drugs listed in Guide 5. These options include chemotherapy and targeted therapy drugs. The treatment options are listed in order of preference of NCCN experts.

After first-line treatment, your doctor may consider maintenance therapy with lenalidomide if you are at high risk for the disease to relapse (return). Your doctor will test for MRD after first-line treatment. MRD is when a very small amount of leukemia cells remains in your body after a course of treatment. With MRD, the amount of leukemia cells left is too small to be seen with a microscope. Thus, further treatment may be given.

Guide 5. First-time treatments including purine analogs

Younger and fairly healthy

<table>
<thead>
<tr>
<th>Treatment options (best options listed first)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FCR</td>
</tr>
<tr>
<td>• Ibrutinib</td>
</tr>
<tr>
<td>• FR (fludarabine, rituximab)</td>
</tr>
<tr>
<td>• Bendamustine ± CD20 monoclonal antibody</td>
</tr>
<tr>
<td>• HDMP + rituximab</td>
</tr>
<tr>
<td>• PCR (pentostatin, cyclophosphamide, rituximab)</td>
</tr>
</tbody>
</table>

NCCN Guidelines for Patients®: Chronic Lymphocytic Leukemia, 2018
Guide 6. Treatments if prior treatment fails

Younger and fairly healthy

<table>
<thead>
<tr>
<th>Treatment options (best options listed first)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ibrutinib</td>
</tr>
<tr>
<td>• Idelalisib + rituximab</td>
</tr>
<tr>
<td>• Venetoclax ± rituximab</td>
</tr>
<tr>
<td>• Idelalisib</td>
</tr>
<tr>
<td>• FCR</td>
</tr>
<tr>
<td>• FC + ofatumumab</td>
</tr>
<tr>
<td>• PCR</td>
</tr>
<tr>
<td>• Bendamustine + rituximab</td>
</tr>
<tr>
<td>• HDMP + rituximab</td>
</tr>
<tr>
<td>• Ofatumumab</td>
</tr>
<tr>
<td>• Obinutuzumab</td>
</tr>
<tr>
<td>• Lenalidomide ± rituximab</td>
</tr>
<tr>
<td>• Alemtuzumab ± rituximab</td>
</tr>
<tr>
<td>• Ibrutinib, bendamustine, rituximab</td>
</tr>
<tr>
<td>• Idelalisib, bendamustine, rituximab</td>
</tr>
</tbody>
</table>

Guide 6 lists treatment options for if the CLL responds but comes back (relapsed), or if the first treatment doesn't work (refractory). This is treatment for relapsed or refractory disease for patients who are younger and fit. Before starting treatment, your doctor may want to test the cancer again. Features of cancer can change over time, so re-testing is needed before starting treatment. Tests of the chromosomes in the cancer cells are advised. These tests include FISH and karyotype. Your doctor will also check for a TP53 mutation.

If the features haven’t changed, ibrutinib alone and idelalisib with rituximab are preferred options. They are preferred due to good results measured in well-designed clinical trials. There are 13 other options in Guide 6 that are listed in order of preference of NCCN experts.

If further treatment is needed, your doctor may suggest you join a clinical trial or consider an allogeneic SCT. The allogeneic SCT is an option if you do not have any serious health problems and your disease is not responding to drugs like ibrutinib or idelalisib.
Guide 7. First-time treatments including purine analogs

Older or quite sick

<table>
<thead>
<tr>
<th>Treatment options (best options listed first)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Obinutuzumab + chlorambucil</td>
</tr>
<tr>
<td>• Ibrutinib</td>
</tr>
<tr>
<td>• Ofatumumab + chlorambucil</td>
</tr>
<tr>
<td>• Rituximab + chlorambucil</td>
</tr>
<tr>
<td>• Bendamustine ± CD20 monoclonal antibody</td>
</tr>
<tr>
<td>• Obinutuzumab</td>
</tr>
<tr>
<td>• HDMP + rituximab</td>
</tr>
<tr>
<td>• Rituximab</td>
</tr>
<tr>
<td>• Chlorambucil</td>
</tr>
</tbody>
</table>

Other options include ofatumumab with chlorambucil, rituximab with chlorambucil, bendamustine with or without CD20 monoclonal antibody (see page 31 for CD20 drugs), obinutuzumab, HDMP and rituximab, rituximab alone, or chlorambucil. Chlorambucil is the least preferred option.

After first-line treatment, your doctor may consider maintenance therapy with lenalidomide if you are at high risk for the disease to relapse (come back). Your doctor will test for MRD after first-line treatment. MRD is when a very small amount of leukemia cells remains in your body after a course of treatment. With MRD, the amount of leukemia cells left is too small to be seen with a microscope. Thus, further treatment may be given.

Guide 7 lists first-time treatment options for older or younger sick people with CLL that isn’t missing parts of chromosome 17 or has a TP53 mutation. Your doctors may think you can withstand purine analogs. However, the first few options listed aren’t as harsh on your body as purine analogs.

Obinutuzumab plus chlorambucil has been the standard of care for this group. It has had good results in well-designed clinical trials. The second drug listed in Guide 7 is ibrutinib. It is also included based on good results in well-designed clinical trials.
Guide 8. Treatments if prior treatment fails

Older or quite sick

<table>
<thead>
<tr>
<th>Treatment options (best options listed first)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ibrutinib</td>
</tr>
<tr>
<td>• Idelalisib + rituximab</td>
</tr>
<tr>
<td>• Venetoclax ± rituximab</td>
</tr>
<tr>
<td>• Idelalisib</td>
</tr>
<tr>
<td>• Reduced-dose FCR</td>
</tr>
<tr>
<td>• Reduced-dose PCR</td>
</tr>
<tr>
<td>• HDMP + rituximab</td>
</tr>
<tr>
<td>• Rituximab + chlorambucil</td>
</tr>
<tr>
<td>• Ofatumumab</td>
</tr>
<tr>
<td>• Obinutuzumab</td>
</tr>
<tr>
<td>• Lenalidomide ± rituximab</td>
</tr>
<tr>
<td>• Alemtuzumab ± rituximab</td>
</tr>
<tr>
<td>• Dose-dense rituximab</td>
</tr>
<tr>
<td>• Bendamustine + rituximab ± ibrutinib</td>
</tr>
<tr>
<td>• Bendamustine + rituximab ± idelalisib</td>
</tr>
</tbody>
</table>

Guide 8 lists treatment options for if the CLL responds but comes back (relapsed), or if the first treatment doesn’t work (refractory). This is treatment for relapsed or refractory disease for patients who are frail or sick, whether young or older. Before starting treatment, your doctor may want to test the cancer again. Features of cancer can change over time, so re-testing may be needed if some time has passed. Tests of the chromosomes in the cancer cells are advised. These tests include FISH and karyotype. Your doctor will also check for a TP53 mutation.

If the features haven’t changed, ibrutinib alone and idelalisib with rituximab are preferred options. They are preferred due to good results measured in well-designed clinical trials. There are 13 other options in Guide 8 that are listed in order of preference of NCCN experts.

If your treatment works, your doctor may consider a stem cell transplant. You must be fairly healthy to have a transplant. A transplant may improve the prognosis of the cancer.

If you have a complete or partial response to treatment for refractory or relapsed disease, your doctor may consider a second maintenance therapy with lenalidomide or ofatumumab. Your doctor will test for MRD and decide on your next steps based on those results. It is helpful to ask your doctor to explain any further treatment options you may have.
Treatment for CLL with del(17p) or $TP53$ mutation

Guide 9. First-time treatments including purine analogs

Guide 9 lists first-time treatment options for CLL that is missing parts of chromosome 17 or has a $TP53$ mutation. A clinical trial is advised. If you can’t join a clinical trial, ibrutinib is the standard of care. Other options include HDMP with rituximab, obinutuzumab, and alemtuzumab with or without rituximab.

If first-time treatment works, treatment may continue with a drug like ibrutinib or idelalisib until the disease progresses. If the disease gets worse, options include a clinical trial, possible allogeneic SCT if you are healthy enough, or other drugs listed in Guide 9.

Another phase of treatment is called maintenance. This phase starts after you are finished first-line treatment. Maintenance therapy is given to keep up (maintain) the good results of prior treatments. The goal is to prevent a relapse after first-line therapy and in some cases, after second-line therapy for CLL with del(17p) or $TP53$ mutation. After first-line treatment, your doctor may consider maintenance therapy with lenalidomide if you are at high risk for the disease to relapse (come back).

Guide 10. Treatments if prior treatment fails

Guide 10 lists treatment options for if the CLL responds but comes back (relapsed), or if the first treatment doesn’t work (refractory). Join a clinical trial if possible. If you are healthy enough your doctor may also consider an allogeneic SCT. He or she may assess the cancer to see if there is a change in the cells such as Richter’s transformation or CLL with progression.

<table>
<thead>
<tr>
<th>Treatment options (best options listed first)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ibrutinib</td>
</tr>
<tr>
<td>• HDMP + rituximab</td>
</tr>
<tr>
<td>• Obinutuzumab</td>
</tr>
<tr>
<td>• Alemtuzumab ± rituximab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment options (best options listed first)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ibrutinib</td>
</tr>
<tr>
<td>• Venetoclax ± rituximab</td>
</tr>
<tr>
<td>• Idelalisib + rituximab</td>
</tr>
<tr>
<td>• Idelalisib</td>
</tr>
<tr>
<td>• HDMP + rituximab</td>
</tr>
<tr>
<td>• Lenalidomide ± rituximab</td>
</tr>
<tr>
<td>• Alemtuzumab ± rituximab</td>
</tr>
<tr>
<td>• Ofatumumab</td>
</tr>
</tbody>
</table>
If you can’t join a clinical trial, ibrutinib is the standard of care. Venetoclax with or without rituximab is another approved option for patients with CLL with del(17p) and who have received prior treatment. Idelalisib can also be given alone or with rituximab as treatment. Other options include HDMP with rituximab, lenalidomide with or without rituximab, alemtuzumab with or without rituximab, and ofatumumab.

If you have a complete or partial response to treatment for refractory or relapsed disease (after second-line therapy), your doctor may consider a second maintenance therapy with lenalidomide or ofatumumab. Your doctor will test for MRD and decide on your next steps based on those results. It is helpful to ask your doctor to explain any further treatment options you may have.

### Richter’s transformation and CLL with progression

About 2 to 10 out of 100 people with CLL will have a change occur in the cells, a transformation that causes a new type of cancer. This is called Richter’s transformation. Richter’s transformation is when CLL becomes a more aggressive lymphoma such as DLBCL or Hodgkin lymphoma. A lymphoma is a hematologic cancer—like leukemia—and this cancer starts in our lymphatic system.

If there is any concern that CLL has transformed, your doctor will recommend additional tests. This may include blood tests as well as imaging such as a PET scan. The PET scan can help your doctor see if it looks like there may be a Richter’s transformation. It can also find the best location to perform a biopsy. The type of biopsy you will have depends on where the lymph node is located and if it can be easily reached. Types of biopsies include an FNA (fine-needle aspiration [small sample is taken]), core needle biopsy (large sample of tissue is taken), and excisional biopsy (removes the whole lymph node). An excisional biopsy is advised if possible.

CLL can also progress and become a more aggressive disease. Progression is the growth or spread of cancer. Thus, your doctor may look at the cells under a microscope to assess for changes (expanded proliferation centers) and study how quickly the cells are growing. A blood test may be done to check for increased prolymphocytes (type of white blood cell) in the blood. This progression is not Richter’s transformation. Your doctor will consider your next steps of care if the disease progresses.
If Richter’s transformation or CLL with progression, more tests will be done before treatment starts. The test results will help your doctor plan your next steps of care. See Guide 11 for a list of tests that must be done and some that may be done in certain cases.

## Guide 11. Care before treatment

<table>
<thead>
<tr>
<th>Must haves</th>
<th>Type of care</th>
<th>Sometimes useful</th>
<th>Type of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Medical history</td>
<td><em>Medical history</em></td>
<td>• Bone marrow aspiration + biopsy</td>
<td>Bone and marrow test</td>
</tr>
<tr>
<td>• Physical exam (including Waldeyer’s ring [tissue inside the throat] and size of the liver and spleen)</td>
<td><em>Exam of the body</em></td>
<td>• Echocardiogram or MUGA</td>
<td><em>Heart test</em></td>
</tr>
<tr>
<td>• Performance status</td>
<td><em>Status of activity level</em></td>
<td>• Hepatitis B testing</td>
<td><em>Blood test</em></td>
</tr>
<tr>
<td>• Complete blood count with differential</td>
<td><em>Blood test</em></td>
<td>• HLA typing</td>
<td><em>Blood test</em></td>
</tr>
<tr>
<td>• Comprehensive metabolic panel</td>
<td><em>Blood test</em></td>
<td>• Pregnancy test if you can have babies</td>
<td><em>Pregnancy test</em></td>
</tr>
<tr>
<td>• LDH</td>
<td><em>Blood test</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Uric acid</td>
<td><em>Blood test</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Check for the Epstein-Barr virus</td>
<td><em>Blood test</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Whole body PET/CT scan or CT scan of the chest, abdomen, and pelvis</td>
<td><em>Imaging test</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Guide 12. First-time treatment options for Richter’s transformation and CLL with progression

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>First-time treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Cancer type</strong></td>
</tr>
<tr>
<td>DLBCL</td>
<td>Cell features not like CLL</td>
</tr>
<tr>
<td></td>
<td>Cell features like CLL</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td></td>
</tr>
<tr>
<td>CLL with progression</td>
<td>• Without del(17p) or TP53 mutation</td>
</tr>
<tr>
<td></td>
<td>• With del(17p) or TP53 mutation</td>
</tr>
</tbody>
</table>

Guide 12 shares first-time treatment of Richter’s transformation and CLL with progression. A clinical trial is advised. If you can’t join a clinical trial, you will have treatment that is recommended for DLBCL and Hodgkin lymphoma, or CLL with progression. Some combinations of drugs including chemotherapy and immunotherapy are listed for DLBCL with cell features similar to CLL.

If you have CLL with progression, you will refer to the guides earlier in this chapter. See the guides listed for CLL without del(17p) or TP53 mutation, or CLL with del(17p) or TP53 mutation. Ask your doctor to share what options are available for disease that progresses.
Guide 13. Further treatment for DLBCL

<table>
<thead>
<tr>
<th>Response to chemotherapy</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy sensitive (chemotherapy is working)</td>
<td>• Consider allogeneic SCT</td>
</tr>
<tr>
<td>Chemotherapy refractory (chemotherapy is not working)</td>
<td>• Clinical trial or • See NCCN Guidelines for B-Cell Lymphomas (treatment for DLBCL)</td>
</tr>
</tbody>
</table>

Guide 13 lists further options after chemotherapy is given for DLBCL. If the chemotherapy is working and you are healthy enough, your doctor may consider an allogeneic SCT. If chemotherapy is not working, your doctor may recommend a clinical trial. For further treatment details, it is also helpful to read the *NCCN Guidelines for Patients*: Diffuse Large B-Cell Lymphoma. These guidelines are available for free at www.nccn.org/patients.
### Supportive care

#### Guide 14. Supportive care by health condition

<table>
<thead>
<tr>
<th>Health condition</th>
<th>Type of supportive care</th>
</tr>
</thead>
</table>
| Severe ear, sinus, or lung infections         | - Medicine as needed  
- Test blood for antibodies  
  ◦ If IgG <500 mg/dL, infusions of gamma globulin every month |
| Flu                                           | - Influenza vaccine every year                                                                                                                         |
| Pneumococcal infection                       | - Vaccine every 5 years; Prevnar is preferred                                                                                                          |
| Blood transfusion needed                     | - Transfusion should be done according to hospital standards  
- All blood products should be radiated        |
| Autoimmune hemolytic anemia                  | - Diagnosis with reticulocyte and haptoglobin counts and direct antitglobulin test  
- If severe, stop taking fludarabine and do not take again  
- Treat with corticosteroids, IVIG, cyclosporin A, splenectomy, or rituximab                      |
| Immune thrombocytopenic purpura              | - Diagnosis with bone marrow test for cause of low platelets  
- Treat with corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim |
| Pure red cell aplasia                        | - Diagnosis with bone marrow test for cause of low platelets  
- Treat with corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim |
| Tumor lysis syndrome                         | - If CLL is present in large amounts and you are at risk:  
  ◦ Consider taking medicine to prevent                                                                                                                |
| Herpes virus                                 | - If receiving purine analogs, bendamustine-based chemotherapy, idelalisib, and/or alemtuzumab:  
  ◦ Start taking medicine like acyclovir to prevent infection                                                                                       |
| Pneumocystis pneumonia                       | - If receiving purine analogs, bendamustine-based chemotherapy, idelalisib, and/or alemtuzumab:  
  ◦ Start taking medicine like sulfamethoxazole and trimethoprim to prevent illness                                                                |
| Cytomegalovirus reactivation                 | - If receiving fludarabine-based chemotherapy, idelalisib, or alemtuzumab:  
  ◦ Start taking ganciclovir if virus is present or rising  
  ◦ Blood tests of virus are needed every 2–3 weeks                                                                                                  |
## Guide 15. Supportive care by health condition

<table>
<thead>
<tr>
<th>Health condition</th>
<th>Type of supportive care</th>
</tr>
</thead>
</table>
| **Hepatitis B** | • If receiving anti-CD20 monoclonal antibodies:  
  ◦ Test to assess status  
  ◦ Start taking medicine to prevent |
| **Hepatitis C (related to B-cell NHL)** | • If chronic (long-term) carrier of hepatitis C virus with genotype 1 (most common type of hepatitis C):  
  ◦ Start taking medicine to prevent |
| **An increase in the size of organs with CLL after starting treatment (ie, tumor flare reactions)** | • If receiving lenalidomide:  
  ◦ Consider preventing flare if large lymph nodes present  
  ◦ Prevent with prednisone 20 mg for 5–7 days then reduce amount over 5–7 days  
  ◦ If flare occurs, treat with prednisone 25–50 mg for 5–10 days  
  ◦ Antihistamines for rash and itching, such as cetirizine 10 mg 4X a day or loratadine 10 mg 1X a day |
| **Blood clot** | • If receiving lenalidomide:  
  ◦ Start taking aspirin 81 mg/day if high number of platelets unless already on warfarin |
| **Irregular, fast heart beat (ie, atrial fibrillation)** | • If receiving ibrutinib:  
  ◦ Consider non-warfarin anticoagulation medicine  
  ◦ If atrial fibrillation can’t be controlled, switch to idelalisib |
| **Serious bleeding** | • If receiving ibrutinib:  
  ◦ Stop taking ibrutinib if on warfarin  
  ◦ Weigh the pros and cons of ibrutinib if on antiplatelet or anticoagulant treatment  
  ◦ Stop ibrutinib before surgery and delay re-starting afterward |
| **Liver damage (ie, hepatotoxicity)** | • If receiving idelalisib:  
  ◦ Stop idelalisib until problem is solved |
| **Diarrhea or swollen colon (ie, colitis)** | • If receiving idelalisib:  
  ◦ Stop idelalisib until problem is solved |
| **Holes in gut** | • If receiving idelalisib:  
  ◦ Stop idelalisib if it is likely causing holes in your gut |
| **Inflammation of the lungs (ie, pneumonitis)** | • If receiving idelalisib:  
  ◦ Stop idelalisib if symptoms appear |
Guides 14 and 15 list some of the supportive care needs of people with CLL. Supportive care doesn’t aim to treat cancer but aims to improve quality of life. It is also called palliative care.

Supportive care can address many needs. It can address emotional and physical needs, such as relieving symptoms. It can also help with treatment decisions as you may have more than one option. Supportive care also includes help with coordination of care between health providers. Talk with your treatment team to plan the best supportive care for you. Supportive care is an important part of your cancer care, especially during active cancer treatment.

You are more likely to get infections due to CLL or its treatment. Some people with CLL get severe ear, sinus, or lung (pneumonia) infections again and again. These infections may require going to the hospital or getting an injection of medicine rather than taking pills. If you get severe infections, testing your antibodies (IgG level) is advised. If your level of IgG is low (<500 mg/dL) and you have severe, recurrent infections, you could benefit by infusions of gamma globulin (IVIG) every month to raise your IgG level above 500 mg/dL.

Some vaccines to prevent illness are advised. Get a flu shot every year and a pneumococcal vaccine every five years. Some vaccines consist of live viruses or bacteria. Do not take live vaccines including the vaccine for shingles or the flu. If you are unsure about a vaccine, ask your treatment team about it.

Some people being treated for CLL will need a blood transfusion. It is very important that the transfusion is done according to hospital standards. All blood should be treated with radiation before the transfusion. This will prevent the new blood from attacking your body.

Autoimmune cytopenias are health conditions in which your immune system becomes confused and reacts against your own blood cells. The most frequent of these among people with CLL are autoimmune hemolytic anemia, immune-mediated thrombocytopenia, and pure red blood cell aplasia. Diagnosis and treatment of these conditions are listed in Guide 14.

Tumor lysis syndrome was described in Part 2. It can occur among people with large amounts of CLL who are undergoing strong cancer treatments. If you are at risk, think about starting medicine to prevent this illness.

Other health conditions listed in Guide 15 are linked to specific cancer treatments. Read through the list to see if any apply to you. Purine analogs are a type of chemotherapy that includes fludarabine, cladribine, and pentostatin. Anti-CD20 monoclonal antibodies include obinutuzumab, ofatumumab, and rituximab.

Risk for other cancers
It is important to talk with your doctor about screening for other cancer. Regular screening for prostate cancer, breast cancer, cervical cancer, and colon cancer is important. People with CLL are also at risk for skin cancer, the non-melanoma type. Being white and having a large amount of contact with the sun at a young age are both risk factors. NCCN recommends you see a dermatologist, a doctor who specializes in skin cancer screening, once a year.
Review

- Treatment options start with a first-line treatment. First-line treatment is the first treatment offered to treat the cancer.

- Treatment options for CLL that isn’t missing parts of chromosome 17 or has TP53 mutations are partly based on age and health status. Obinutuzumab with chlorambucil, ibrutinib, and ofatumumab with chlorambucil are the preferred options.

- Treatment options for CLL that is missing parts of chromosome 17 or has TP53 mutations are based on your health status and may include purine analogs. A clinical trial is preferred followed by ibrutinib.

- Your doctor will re-test to assess FISH, karyotype, and TP53 mutation status after you have treatment and the CLL responds but returns (relapsed) or doesn’t respond well (refractory).

- A small number of people with CLL can develop Richter’s transformation. CLL can also progress.

- People with CLL often need care for health conditions related to the cancer or cancer treatment. Treatment for conditions other than cancer is part of supportive care.

Approach your “recovery” in whatever way you deem best for your situation. Allow yourself to heal. Be positive and stay proactive.

- Ted
Having cancer is very stressful. While absorbing the fact that you have cancer, you have to learn about tests and treatments. In addition, the time you have to accept a treatment plan feels short. Parts 1 through 4 described the cancer and the test and treatment options recommended by NCCN experts. These options are based on science and agreement among NCCN experts. Part 5 aims to help you make decisions that are in line with your beliefs, wishes, and values.

It’s your choice

The role patients want in choosing their treatment differs. You may feel uneasy about making treatment decisions. This may be due to a high level of stress. It may be hard to hear or know what others are saying. Stress, pain, and drugs can limit your ability to make good decisions. You may feel uneasy because you don’t know much about cancer. You’ve never heard the words used to describe cancer, tests, or treatments. Likewise, you may think that your judgment isn’t any better than your doctors’.

Letting others decide which option is best may make you feel more at ease. However, whom do you want to make the decisions? You may rely on your doctors alone to make the right decisions. However, your doctors may not tell you which to choose if you have multiple good options. You can also have loved ones help. They can gather information, speak on your behalf, and share in decision-making with your doctors. Even if others decide which treatment you will receive, your treatment team may still ask that you sign a consent form.

On the other hand, you may want to take the lead or share in decision-making. In shared decision-making, you and your doctors share information, discuss the options, and agree on a treatment plan. Your doctors know the science behind your plan but you know your concerns and goals. By working together, you can decide on a plan that works best for you when it comes to your personal and health needs.

Questions to ask your doctors

You will likely meet with experts from different fields of medicine. It is helpful to talk with each person. Prepare questions before your visit and ask questions if the information isn’t clear. You can get copies of your medical records. It may be helpful to have a family member or friend with you at these visits to listen carefully and even take notes. A patient advocate or navigator might also be able to come. They can help you ask questions and remember what was said.

The questions below are suggestions for information you read about in this book. Feel free to use these questions or come up with your own personal questions to ask your doctor and other members of your treatment team.
What’s my diagnosis and prognosis?

It’s important to know that there are different types of cancer. Cancer can greatly differ even when people have a tumor in the same organ. Based on your test results, your doctors can tell you which type of cancer you have. He or she can also give a prognosis. A prognosis is a prediction of the pattern and outcome of a disease. Knowing the prognosis may affect what you decide about treatment.

1. Where did the cancer start? In what type of cell?
2. Is this cancer common?
3. What is the cancer stage? Does this stage mean the cancer has spread far?
4. Is this a fast- or slow-growing leukemia?
5. What other tests results are important to know?
6. How often are these tests wrong?
7. Would you give me a copy of the pathology report and other test results?
8. Can the cancer be cured? If not, how well can treatment stop the cancer from growing?
What are my options?

There is no single treatment practice that is best for all patients. There is often more than one treatment option along with clinical trial options. Your doctor will review your test results and recommend treatment options.

1. What will happen if I do nothing?

2. Can I just carefully monitor the cancer?

3. Do you consult NCCN recommendations when considering options?

4. Are you suggesting options other than what NCCN recommends? If yes, why?

5. Do your suggested options include clinical trials? Please explain why.

6. How do my age, health, and other factors affect my options?

7. Which option is proven to work best?

8. Which options lack scientific proof?

9. What are the benefits of each option? Does any option offer a cure? Are my chances any better for one option than another? Less time-consuming? Less expensive?

10. What are the risks of each option? What are possible complications? What are the rare and common side effects? Short-lived and long-lasting side effects? Serious or mild side effects? Other risks?

11. What can be done to prevent or relieve the side effects of treatment?
What does each option require of me?

Many patients consider how each option will practically affect their lives. This information may be important because you have family, jobs, and other duties to take care of. You also may be concerned about getting the help you need. If you have more than one option, choosing the option that is the least taxing may be important to you.

1. Will I have to go to the hospital or elsewhere? How often? How long is each visit?

2. Do I have a choice of when to begin treatment? Can I choose the days and times of treatment?

3. How do I prepare for treatment? Do I have to stop taking any of my medicines? Are there foods I will have to avoid?

4. Should I bring someone with me when I get treated?

5. Will the treatment hurt?

6. How much will the treatment cost me? What does my insurance cover?

7. Will I miss work or school? Will I be able to drive?

8. Is home care after treatment needed? If yes, what type?

9. How soon will I be able to manage my own health?

10. When will I be able to return to my normal activities?
What is your experience?

More and more research is finding that patients treated by more experienced doctors have better results. It is important to learn if a doctor is an expert in the cancer treatment he or she is offering.

1. Are you board certified? If yes, in what area?

2. How many patients like me have you treated?

3. How many procedures like the one you’re suggesting have you done?

4. Is this treatment a major part of your practice?

5. How many of your patients have had complications?
Deciding between options

Deciding which option is best can be hard. Doctors from different fields of medicine may have different opinions on which option is best for you. This can be very confusing. Your spouse or partner may disagree with which option you want. This can be stressful. In some cases, one option hasn’t been shown to work better than another, so science isn’t helpful. Some ways to decide on treatment are discussed next.

Getting a 2nd opinion
Even if you like and trust your doctor, it is helpful to get a 2nd opinion. You will want to have another doctor review your test results. He or she can suggest a treatment plan or check the one you already heard about.

Things you can do to prepare:

- Check with your insurance company about its rules on 2nd opinions. You want to know about out-of-pocket costs for doctors who are not part of your insurance plan.

- Make plans to have copies of all your records sent to the doctor you will see for your 2nd opinion. Do this well before your appointment. If you run into trouble having records sent, pick them up and bring them with you.

If the new doctor offers other advice, make an appointment with your first doctor to talk about the differences. Do whatever you need to feel confident about your diagnosis and treatment plan.

Getting support
Support groups often include people at different stages of treatment. Some may be in the process of deciding while others may be finished with treatment. At support groups, you can ask questions and hear about the experiences of other people with CLL. If your hospital or community doesn’t have support groups for people with CLL, check out the websites on the next page.

You can also reach out to a social worker or psychologist. They can help you find ways to cope or refer you to support services. These services may also be available to your family, friends, and to those with children, so they can connect and get support.

Keep in mind...

✓ Every treatment option has benefits and risks. Consider these when deciding which option is best for you.
✓ Talking to others may help identify benefits and risks you haven’t thought of.
Websites

American Cancer Society
cancer.org/cancer/leukemia-chroniclymphocyticcll/index

CLL Society Inc. (CLLS)
cllsociety.org

National Cancer Institute
cancer.gov/types/leukemia

National Coalition for Cancer Survivorship
canceradvocacy.org/toolbox

NCCN
nccn.org/patients

The Leukemia & Lymphoma Society (LLS)
LLS.org/InformationSpecialists

Review

- Shared decision-making is a process in which you and your doctors plan treatment together.

- Asking your doctors questions is vital to getting the information you need to make informed decisions.

- Getting a 2\textsuperscript{nd} opinion, attending support groups, and comparing benefits and risks may help you decide which treatment is best for you.

"Meeting with and learning from other CLL patients is one of the best sources of emotional and educational support that I have seen. In a CLL support group we can share our feelings, experiences, and encouragement with the only ones who are able to see CLL from the inside out - the patients!"

- Barbara
Dictionary

**alkylating agent**
A class of chemotherapy that works by inserting a toxic chemical inside of cells to kill them.

**allogeneic stem cell transplant**
A cancer treatment that suppresses bone marrow then replaces it by adding healthy blood stem cells from a donor.

**anemia**
Abnormal low numbers of healthy red blood cells.

**anesthesia**
Loss of feeling with or without loss of wakefulness that is caused by drugs.

**antibody**
A protein made by white blood cells that helps fight off infection. Also called an immunoglobulin.

**antigen**
Any substance that activates the immune system.

**autoimmune hemolytic anemia**
The wrongful destruction of red blood cells by the immune system.

**B symptoms**
High fevers, heavy night sweats, and fast weight loss without dieting caused by B-cell cancers.

**B-cell**
One of three types of a white blood cell called a lymphocyte.

**beta-2 microglobulin**
A small protein made by many types of cells.

**biopsy**
Removal of small amounts of tissue or fluid to be tested for disease.

**bone marrow**
Soft, sponge-like tissue in the center of most bones where blood cells are made.

**bone marrow aspirate**
Removal of a small amount of bone marrow that is liquid to test for disease.

**bone marrow biopsy**
Removal of a small amount of solid bone and bone marrow to test for disease.

**cancer stages**
Ratings of tumors that suggest the outlook of the disease.

**chemotherapy**
Drugs that stop the life cycle of cells so they don’t increase in number.

**chromosome**
Stands of genetic material inside of cells.

**clinical trial**
Research on a test or treatment to assess its safety or how well it works.

**Coombs test**
A lab test that detects if antibodies are stuck to and destroying red blood cells.

**complete blood count (CBC)**
A test of the number of blood cells in a sample.

**comprehensive metabolic panel**
Tests of about 14 chemicals in your blood.

**computed tomography (CT)**
A test that uses x-rays to view body parts.

**contrast**
A dye put into your body to make clearer pictures during imaging tests.

**deoxyribonucleic acid (DNA)**
A chain of chemicals inside cells that contains coded instructions for making and controlling cells.

**deoxyribonucleic acid (DNA) sequencing**
A lab test used to look for abnormal changes in DNA.

**diagnose**
To identify a disease.
**differential**
Measurement of the different types of white blood cells present in a blood sample.

**echocardiogram**
A test that uses sound waves to make pictures of the heart.

**fatigue**
Severe tiredness despite getting enough sleep that limits one's ability to function.

**fertility specialist**
An expert who helps men and women have babies.

**flow cytometry**
A test that looks at certain substances on the surface of cells to identify the type of cells present.

**fluorescence in situ hybridization (FISH)**
A lab test that uses special dyes to look for abnormal chromosomes.

**gene**
Instructions in cells for making and controlling cells.

**graft-versus-leukemia (GVL) effect**
An attack on cancer cells by transplanted stem cells from a donor.

**haptoglobin**
One of the proteins made by the liver.

**hemoglobin**
A protein with iron that is released from destroyed red blood cells.

**hemolysis**
The early death of red blood cells.

**human leukocyte antigen (HLA) typing**
A blood test that finds a person's unique set of proteins on cells.

**imaging test**
A test that makes pictures (images) of the inside of the body.

**immune system**
The body's natural defense against disease.

**immunoglobulin**
A protein made by white blood cells that helps fight off infection. Also called an antibody.

**immunohistochemistry (IHC)**
A test of cancer cells to find specific cell traits involved in abnormal cell growth.

**immunomodulator**
A type of drug that modifies some parts of the body's disease-fighting system.

**lactate dehydrogenase**
A protein that helps to make energy in cells.

**liver**
Organ that removes waste from the blood and helps to digest food.

**local anesthesia**
A controlled loss of feeling in a small area of the body caused by drugs.

**lymph**
A clear fluid containing white blood cells.

**lymph node**
Small groups of special disease-fighting cells located throughout the body.

**lymph vessel**
Tube-shaped ducts that carry lymph throughout the body.

**lymphatic system**
A network in the body that collects and transports a fluid (lymph) and fights germs.

**lymphocyte**
A type of white blood cell that helps protect the body from illness.

**lymphoma**
Cancer that begins in white blood cells called lymphocytes that are within the lymphatic system.

**karyotyping**
A test that uses a microscope to examine a cell's chromosomes.

**kinase inhibitors**
Cancer treatment that stops the transfer of phosphates, which blocks growth signals to cancer cells.

**mantle cell lymphoma**
A cancer that is defined by too many proteins called cyclin D1.

**medical history**
All health events and medications taken to date.

**methylation analysis**
A lab test that looks for chemical tags, called methyl groups, on DNA.
**monoclonal antibody**  
Man-made antibodies that attach proteins on cancer cells.

**monoclonal B-lymphocytosis (MBL)**  
A health condition that features high numbers of B-cells but is not cancer.

**multi-gated acquisition (MUGA) scan**  
A test of the heart that uses radiation to make pictures.

**natural killer (NK) cell**  
One of three types of a white blood cell called a lymphocyte.

**observation**  
A period of testing for changes in cancer status while not receiving a specific treatment.

**pathologist**  
A doctor who’s an expert in testing cells to find disease.

**performance status**  
A rating of one’s ability to do daily activities.

**physical exam**  
A review of the body by a health expert for signs of disease.

**positron emission tomography (PET)**  
A test that uses radioactive material to see the shape and function of body parts.

**prognosis**  
The expected pattern and outcome of a disease based on tests.

**pure red cell aplasia**  
Very low numbers of the precursor cells to red blood cells in bone marrow.

**purine analogs**  
A type of chemotherapy that increases the likelihood of serious infections.

**Rai staging system**  
The system used to stage chronic lymphocytic leukemia.

**reticulocytes**  
Precursor cells to mature red blood cells.

**Richter’s transformation**  
Cellular level transformation of chronic lymphocytic leukemia to diffuse large B-cell lymphoma or Hodgkin lymphoma.

**sedative**  
A drug that helps a person to relax or go to sleep.

**side effect**  
An unplanned physical or emotional response to treatment.

**spleen**  
An organ to the left of the stomach that helps protect the body from disease.

**stem cell transplant**  
A cancer treatment that destroys bone marrow then replaces it by adding healthy blood stem cells.

**steroid**  
A drug used to reduce redness, swelling, and pain, but also to kill cancer cells.

**supportive care**  
Treatment for the symptoms or health conditions caused by cancer or cancer treatment.

**targeted therapy**  
Drugs that stop the growth process that is specific to cancer cells.

**T-cell**  
One of three types of a white blood cell called a lymphocyte.

**thymus**  
A gland located in the throat, just beneath the voice box.

**tonsil**  
A group of tissue within the throat that contains many white blood cells called lymphocytes and fights germs that enter the mouth and nose.

**tumor lysis syndrome (TLS)**  
A condition that occurs when many cancer cells die very quickly and release their contents into the blood, which can damage the kidneys and other organs.

**ultrasound**  
A test that uses sound waves to take pictures of the inside of the body.

**uric acid**  
A chemical that is made and released into the blood when cells and other substances in the body break down.

**vaccine**  
A biological agent inserted into the body to prevent a disease.
Acronyms

BTK
Bruton’s tyrosine kinase

CAM
complementary and alternative medicine

CBC
complete blood count

CLL
chronic lymphocytic leukemia

CT
computed tomography

CVC
central venous catheter

DLBCL
diffuse large B-cell lymphoma

DNA
deoxyribonucleic acid

FDA
U.S. Food and Drug Administration

FISH
fluorescence in situ hybridization

FNA
fine needle aspiration

GVL
graft-versus-leukemia

HLA
human leukocyte antigen

IGHV
immunoglobulin heavy-chain variable

IHC
immunohistochemistry

MBL
monoclonal B-lymphocytosis

MUGA
multi-gated acquisition

NK cells
natural killer cells

PET
positron emission tomography

PI3K
phosphoinositide 3-kinase delta

SLL
small lymphocytic leukemia

TLS
tumor lysis syndrome
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- Follicular Lymphoma
- Mantle Cell Lymphoma
- Mycosis Fungoides
- Peripheral T-cell Lymphoma
- Ovarian Cancer
- Pancreatic Cancer
- Prostate Cancer
- Rectal Cancer
- Soft Tissue Sarcoma
- Stomach Cancer
- Thyroid Cancer
- Waldenström’s Macroglobulinemia/ Lymphoplasmacytic Lymphoma

Translations:
- Kidney Cancer
- Chinese
- Czech
- German
- Spanish

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