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PATIENT AND CARE PROVIDER INFORMATION

CHRONIC LYMPHOCYTIC LEUKEMIA: Expert Guidance for Treatment Selection
www.clinicaloptions.com/CLLtool

https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/detection-diagnosis-staging/signs-symptoms.html

Signs and Symptoms of Chronic Lymphocytic Leukemia

Many people with chronic lymphocytic leukemia (CLL) do not have any symptoms when it is diagnosed. The leukemia is often found when their doctor orders blood tests for some unrelated health problem or during a routine check-up and they are found to have a high number of lymphocytes.

Even when people with CLL have symptoms, they're often vague and can be symptoms of other things. Symptoms can include the following:

- Weakness
- Fatigue
- Weight loss
- Chills
- Fever
- Night sweats
- Lymphadenopathy
- Splenomegaly: Pain or a sense of "fullness" in the belly (this can make someone feel full after only a small meal), which is caused by an enlarged spleen and/or liver

Many of the signs and symptoms of advanced CLL occur because the leukemia cells replace the bone marrow's normal blood-making cells. As a result, people don't have enough red blood cells, properly functioning white blood cells, and blood platelets.

- **Anemia** is a shortage of red blood cells. It can cause tiredness, weakness, and shortness of breath.
- **A shortage of normal white blood cells (leukopenia) increases the risk of infections.** You might hear the term **neutropenia**, which refers to low levels of neutrophils (a type of granulocyte needed to fight bacterial infections). People with CLL may have very high white blood cell counts

because of excess numbers of lymphocytes (**lymphocytosis**), but the leukemia cells don't fight infection the way normal white blood cells do.

- **A shortage of blood platelets (thrombocytopenia) can lead to excess bruising, bleeding, frequent or severe nosebleeds, and bleeding gums.**

People with CLL have a higher risk of infections. This is mainly because their immune systems aren't working as well as they should. CLL is a cancer of B lymphocytes, which normally make antibodies that help fight infection. Because of the CLL, these antibody-making cells don't work as they should, so they can't fight infections. Infections may range from simple things like frequent colds or cold sores to pneumonia and other serious infections.

CLL can also affect the immune system in other ways. In some people with CLL, the immune system cells make abnormal antibodies that attack normal blood cells. This is known as **autoimmunity**. It can lead to low blood counts. If the antibodies attack red blood cells, it's called **autoimmune hemolytic anemia**. Less often, the antibodies attack platelets and the cells that make them, leading to low platelet counts. Rarely, the antibodies attack white blood cells, leading to leukopenia (low white blood cell counts).

These symptoms and signs may be caused by CLL, but they can also be caused by other conditions. Still, if you have any of these problems, it's important to see a doctor right away so the cause can be found and treated, if needed

https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/treating/treatment-by-risk-group.html

Typical Treatment of Chronic Lymphocytic Leukemia

CLL mainly affects older adults. The average age at the time of diagnosis is around 70years. It's rarely seen in people under age 40, and is extremely rare in children.

Treatment options for chronic lymphocytic leukemia (CLL) vary greatly, depending on the person's age, the disease risk group, and the reason for treating (for example, which symptoms it is causing). Many people live a long time with CLL, but in general it is very difficult to cure, and early treatment hasn't been shown to help people live longer. Because of this and because treatment can cause side effects, doctors often advise waiting until the disease is progressing or bothersome symptoms appear, before starting treatment.

If treatment is needed, factors that should be taken into account include the patient's age, general health, and prognostic factors such as the presence of deletions in chromosomes 17 or 11, or high levels of ZAP-70 and CD38.

Initial treatment of CLL

Drugs that may be used

Patients who might not be able to tolerate the side effects of strong chemotherapy (chemo) are often treated with chlorambucil with a monoclonal antibody like obinutuzumab (Gazyva). Other options include the targeted drug ibrutinib (Imbruvica) alone, and rituximab alone or with a corticosteroid like prednisone.

There are other options, too.

In stronger and healthier patients, commonly used treatments include:

- FCR: fludarabine (Fludara), cyclophosphamide (Cytoxan), and rituximab
- Bendamustine (sometimes with a CD20 monoclonal antibody)
- Ibrutinib (alone or with obinutuzumab)
- FR: fludarabine and rituximab
- High-dose prednisone and rituximab
- PCR: pentostatin (Nipent), cyclophosphamide, and rituximab
- Alemtuzumab (Campath) with rituximab

Other drugs or combinations of drugs may also be used.

Radiation or surgery

If the only problem is an enlarged spleen or swollen lymph nodes in one part of the body, localized treatment with low-dose radiation therapy may be used. Splenectomy (surgery to remove the spleen) is another option if the enlarged spleen is causing symptoms.

Leukapheresis

Sometimes very high numbers of CLL cells in the blood cause problems with normal circulation. This is called **leukostasis**. Chemo may not lower the number of cells until a few days after the first dose, so before the chemo is given, some of the cells may need to be removed from the blood with a procedure called **leukapheresis**. This treatment lowers blood counts right away. The effect lasts only for a short time, but it may help until the chemo has a chance to work. Leukapheresis is also sometimes used before chemo if there are very high numbers of leukemia cells (even when they aren't causing problems) to prevent tumor lysis syndrome. (This was discussed in the chemotherapy section.)

Stem cell transplant

Some people who have very high-risk disease (based on prognostic factors) may be referred for possible stem cell transplant (SCT) early in treatment.

Second-line treatment of CLL

If the initial treatment is no longer working or the disease comes back, another type of treatment often helps. If the initial response to the treatment lasted a long time (usually at least a few years), the same treatment might be used again. If the initial response wasn't long-lasting, using the same treatment isn't as likely to be helpful. The options will depend on what the first-line treatment was and how well it worked, as well as the person's overall health.

Many of the drugs and combinations listed above may be options as second-line treatments, too. Targeted therapy and monoclonal antibody drugs are commonly used, alone or in combination. Other chemo drugs may also be tried.

If the leukemia responds, stem cell transplant may be an option for some patients.

Some people may have a good response to first-line treatment (such as fludarabine) but may still have some evidence of a small number of leukemia cells in the blood, bone marrow, or lymph nodes. This is known as **minimal residual disease.** CLL can't be cured, so doctors aren't sure if further treatment right away will be helpful. Some small studies have shown that alemtuzumab can sometimes help get rid of these remaining cells, but it's not yet clear if this improves survival.

Treating complications of CLL : One of the most serious complications of CLL is a change (transformation) of the leukemia to a high-grade or aggressive type of non-Hodgkin lymphoma (NHL) called diffuse large B-cell lymphoma (DLBCL) or to Hodgkin lymphoma. This happens in 2% to 10% of CLL cases, and is known as Richter's transformation. Treatment is often the same as it would be for lymphoma and might include stem cell transplant, because these cases are often hard to treat.

Less often, CLL may progress to prolymphocytic leukemia. As with Richter syndrome, this, too, can be hard to treat. Some studies have suggested that certain drugs such as cladribine (2-CdA) and alemtuzumab may be helpful.

In rare patients with CLL, the leukemia transforms into acute lymphocytic leukemia (ALL). If this happens, treatment is likely to be similar to that used for patients with ALL.

Acute myeloid leukemia (AML) is another rare complication in patients who have been treated for CLL. Drugs such as chlorambucil and cyclophosphamide can damage the DNA of blood-forming cells. These damaged cells may go on to become cancer, leading to AML, which is very aggressive and often hard to treat.

CLL can cause problems with low blood counts and infections.

Newer Therapies: Vaccines, CAR-T cell therapy

Supportive Care for Chronic Lymphocytic Leukemia

https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/treating/supportive-care.html

Supportive care for chronic lymphocytic leukemia (CLL) is aimed at helping with problems related to the cancer and its treatment. It's not treatment for the CLL itself. For instance, some people with CLL have problems with infections or low blood counts. Although treating the CLL may help these over time, other treatments may be needed in the meantime.

Treatments to prevent infections

Intravenous immunoglobulin (IVIG)

Some people with CLL don't have enough antibodies (immunoglobulins) to fight infection. This can lead to repeated lung and/or sinus infections. Antibody levels can be checked with a blood test, and if they're low, antibodies from donors can be given into a vein (IV) to raise the levels and help prevent infections. These donated antibodies are called intravenous immunoglobulin or IVIG. IVIG is often given once a month at first, but can also be given as needed based on blood tests of antibody levels.

Antibiotics and anti-virals

Certain chemo drugs (such as purine analogs – see the chemotherapy section for details) and the antibody drug alemtuzumab (Campath) can raise your risk of certain infections such as CMV (a virus) and pneumonia caused by *Pneumocystis jiroveci*. You might be given an anti-viral drug like acyclovir or valacyclovir (Valtrex®) to help lower the risk of CMV infections. To help prevent Pneumocystis pneumonia, a sulfa antibiotic is often given (trimethoprim with sulfamethoxazole, which is often known by the brand names Septra® or Bactrim®). Other treatments are available for people who are allergic to sulfa drugs.

Some drugs used to treat CLL can also cause dormant viruses to become active. For instance, if you already carry the hepatitis virus or CMV, treatment may allow them to grow and cause problems. Blood tests will be done to watch virus levels. Drugs may be used to help keep these viruses under control.

Using drugs to help prevent infections this way may be called anti-infective prophylaxis. Antibiotics and anti-viral drugs are also used to treat infections. Often, active infections require higher doses or different drugs than are used to prevent infections.

Routine Vaccines (opinion of conventional oncology hematologyy)

It's best for people with CLL to speak to their health care provider before getting any vaccine.

Experts recommend that people with CLL get the pneumonia vaccine every 5 years. They also recommend a yearly flu shot (influenza vaccine).

Avoid vaccines that contain live viruses.

For more information on vaccines, see Vaccination During Cancer Treatment.

Treatments for low blood counts

CLL or its treatment can cause low blood cell counts . Low red blood counts cause anemia. Anemia can make you feel tired, light headed, or short of breath from walking. If anemia is causing symptoms, it can be treated with transfusions. These are often given in an outpatient clinic. If platelet counts get very low, it can lead to serious bleeding. Platelet transfusions can help prevent this.

In CLL, low red blood and platelet counts can also be caused by the cells being destroyed by abnormal antibodies. When antibodies cause low numbers of platelets, it's called **immune thrombocytopenic purpura** or ITP. Before diagnosing this, the doctor often needs to check the bone marrow to make sure that there isn't another cause for the low platelet counts. In ITP, giving platelet transfusions doesn't usually help increase the platelet counts much, if at all, because the antibodies just destroy the new platelets, too. This can be treated by drugs that affect the immune system, like corticosteroids, IVIG, and the antibody drug rituximab (Rituxan®). Another option is to remove the spleen , since after the antibodies stick to the platelets, they're actually destroyed in the spleen. Another option is a drug that tells the body to make more platelets, like eltrombopag (Promactac®) or romiplostim (Nplate®).

When antibodies cause low red blood cell counts, it's called **autoimmune hemolytic anemia** (AIHA). This also can be treated with drugs that affect the immune system, like corticosteroids, IVIG, and rituximab (Rituxan). Removing the spleen is another option. If you develop AIHA while taking fludarabine (Fludara®), the drug may be the cause so it will be stopped.

- References

https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/detection-diagnosis-staging/staging.html

How is Chronic Lymphocytic Leukemia Staged?

For most cancers, staging is the process of finding out how far the cancer has spread. Stages are often useful because they can help guide treatment and determine a person's outlook. Most types of cancer are staged based on the size of the tumor and how far the cancer has spread.
Chronic lymphocytic leukemia (CLL), on the other hand, does not usually form tumors. It's generally in the bone marrow and blood. And, in many cases, it has spread to other organs such as the spleen, liver, and lymph nodes by the time it's found. The outlook for a person with CLL depends on other information, such as the results of lab test and imaging tests.

Staging systems for chronic lymphocytic leukemia

A staging system is a standard way for the cancer care team to describe cancer. There are 2 different systems for staging CLL:

- **Rai system:** This is used more often in the United States.
- **Binet system:** This is used more widely in Europe.
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Both of these staging systems are helpful and have been in use for many years.

Rai staging system

The Rai system is based on lymphocytosis. The patient must have a high number of lymphocytes in their blood and bone marrow that isn't linked to any other cause (like infection).
For a diagnosis of CLL, the overall lymphocyte count does not have to be high, but the patient must have at least 5,000/mm3 monoclonal lymphocytes (sometimes called a monoclonal lymphocytosis).

Monoclonal means that the cancer cells all came from one original cell. This causes them to have the same chemical pattern which can be seen with special testing.
This system divides CLL into 5 stages based on the results of blood tests and a physical exam:

- **Rai stage 0:** Lymphocytosis; no enlargement of the lymph nodes, spleen, or liver; red blood cell and platelet counts are near normal.
- **Rai stage I:** Lymphocytosis; enlarged lymph nodes; spleen and liver are not enlarged; red blood cell and platelet counts are near normal.
- **Rai stage II:** Lymphocytosis; enlarged spleen (and maybe an enlarged liver); lymph nodes may or may not be enlarged; red blood cell and platelet counts are near normal.
- **Rai stage III:** Lymphocytosis; lymph nodes, spleen, or liver may or may not be enlarged; red blood cell counts are low (anemia); platelet counts are near normal.
- **Rai stage IV:** Lymphocytosis; enlarged lymph nodes, spleen, or liver; red blood cell counts may be low or near normal; platelet counts are low (thrombocytopenia).
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Doctors separate the Rai stages into low-, intermediate-, and high-risk groups when determining treatment options.

- Stage 0 is low risk.
- Stages I and II are intermediate risk.
- Stages III and IV are high risk.

These risk groups are used later in Treatment of Chronic Lymphocytic Leukemia.

Binet staging system
In the Binet staging system, CLL is classified by the number of affected lymphoid tissue groups (neck lymph nodes, groin lymph nodes, underarm lymph nodes, spleen, and liver) and by whether or not the patient has anemia (too few red blood cells) or thrombocytopenia (too few blood platelets).

- **Binet stage A:** Fewer than 3 areas of lymphoid tissue are enlarged, with no anemia or thrombocytopenia.
- **Binet stage B:** 3 or more areas of lymphoid tissue are enlarged, with no anemia or thrombocytopenia.
- **Binet stage C:** Anemia and/or thrombocytopenia are present. Any number of lymphoid tissue areas may be enlarged.

Prognostic factors for chronic lymphocytic leukemia

Along with the stage, there are other factors that help predict a person's outlook. These factors are not part of formal staging systems (at least at this time), but are often taken into account when looking at possible treatment options.

- Factors that tend to be linked with shorter survival time are called **adverse prognostic factors**.
- Those that predict longer survival are **favorable prognostic factors**.

Adverse prognostic factors

- Diffuse pattern of bone marrow involvement (more widespread replacement of normal marrow by leukemia)
- Advanced age
- Deletions of parts of chromosomes 17 or 11
- Trisomy 12 in the CLL cells
- High blood levels of certain substances, such as beta-2-microglobulin

- Lymphocyte doubling time (the time it takes for the lymphocyte count to double) of less than 1 year
- Increased fraction of prolymphocytes (an early form of the lymphocyte) in the blood
- High proportion of CLL cells containing ZAP-70 (20% or more) or CD38 (30% or more)
- CLL cells with unchanged (not mutated) gene for the immunoglobulin heavy chain variable region (IGHV)
- CLL cells don't have the TP53 gene
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Favorable prognostic factors

- Non-diffuse (nodular or interstitial) pattern of bone marrow involvement
- Deletion of part of chromosome 13 (with no other chromosome abnormalities)
- Low proportion of CLL cells containing ZAP-70 (less than 20%) or CD38 (less than 30%)
- CLL cells with a mutated gene for IGHV
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Certain prognostic factors such as the presence or absence of ZAP-70, CD38, and a mutated gene for IGHV help divide cases of CLL into 2 groups, slow growing and fast growing. People with the slower growing kind of CLL tend to live longer and may be able to delay treatment longer as well.