



BEFORE TREATMENT

A person with CLL should be treated by a **hematologist-oncologist**. This type of doctor specializes in treating patients who have leukemia. He or she will discuss the most appropriate treatment options for you, including whether or not participation in a clinical trial is recommended.

Speak to your doctor about **treatment sequencing** (the determination of the best first-line treatment and order of additional therapies once treatment begins).

Speak to your doctor or healthcare team about the **cost of treatment** and how long treatment will last. Once these factors are understood, you can begin to plan about how to pay for this treatment.

- Call The Leukemia & Lymphoma Society's Information Specialists for tips on how to speak to your doctor about cost of treatment and ideas on ways to pay for your treatment.

Receive the correct testing before starting therapy, including

- Cytogenetic testing (FISH testing) to determine if any mutations are present such as deletion of the short arm of chromosome 17 (del[17p]) or del(11q). If this test was not done at the time of the initial diagnosis, it should be done now. If previous testing was done months or years ago, this test should be repeated.
- An assessment of *IgHV* gene mutational status
- Testing for prior hepatitis B exposure
- A bone marrow aspiration and biopsy
- A direct antibody test (DAT, also known as the “direct Coombs test”).

TYPES OF TREATMENT

For patients with low risk, non-symptomatic CLL

The watch-and-wait approach

This treatment approach means that your hematologist-oncologist will regularly observe your condition during physical exams and will order lab tests. You will not be treated with drugs or other therapies during the watch and wait period.

- Are you concerned that you will not begin treatment right away?

The watch-and-wait approach is the current standard of care for this group of patients. This approach can be a scary and counter intuitive. Many people are diagnosed with cancer and they begin drug treatment right away. CLL can be a very slow-moving disease and many patients will not have enough disease to warrant treatment with drugs at the time of diagnosis. To date, no benefits of early drug treatment for people with low-risk CLL have been shown.

For patients with symptomatic CLL

Your doctor will begin treatment when

- The CLL starts progressing rapidly
- You have significant symptoms that become bothersome to your quality of life
- Symptoms are risking your health (for example, low platelets).

Some important factors in determining the choice of treatment are:

The presence or absence of del(17p). This is essential information because the deletion of the short arm of chromosome 17 (del[17p]) is associated with a less favorable prognosis and resistance to chemotherapy.

Your fitness category. CLL is typically diagnosed in elderly patients so an evaluation of a patient's fitness and the identification of other medical conditions or problems (comorbidities) that may affect CLL treatment is very important.

THE FIT CATEGORY: CLL Patients Younger Than 65 to 70 Years Without del(17p)

Younger patients in the fit category typically have no significant comorbidities and are eligible for intensive chemoimmunotherapy. These patients are generally treated with a chemotherapy combination called FCR (fludarabine [Fludara®], cyclophosphamide [Cytoxan®] and rituximab [Rituxan®]). This therapy is very effective at reducing disease and, for most patients, the treatment is tolerable as it has very few side effects. Studies have shown that this combination is particularly effective in patients with the *IgHv* gene mutation.

Treatment with FCR has become the standard of care for this group of patients. Results from longer follow-up studies have shown that a significant number of patients that received this therapy remain without detectable disease 10 years after the end of treatment. However, there are some complications associated with this therapy. Some studies have indicated a higher incidence of neutropenia (low numbers of neutrophils leading to greater risk of infection) and a more frequent occurrence of viral and bacterial infections for up to 2 years after the completion of treatment.

Other treatments that have been approved for this group of patients include the following:

- Ibrutinib (Imbruvica®) in combination with bendamustine and rituximab (BR)
- Ibrutinib in combination with obinutuzumab (Gazyva®)
- Bendamustine hydrochloride (Bendeka®)

OLDER OR LESS FIT CATEGORY: CLL Patient Older Than 65 to 70 Years Without del(17p).

For some fit patients that fall into this age category, the combination of bendamustine (Bendeka®) with rituximab (Rituxan®) (BR) may be a good option.

Older patients or patients with significant comorbidities are considered to be in the less fit category. Studies have shown that fludarabine-based treatment is not well tolerated in older patients and it becomes even less effective as patient age increases to 70 years and older.

Typically, patients in this category are treated with combination chemoimmunotherapy using an oral drug called "chlorambucil," which is better tolerated than fludarabine in older patients. Chlorambucil is given together with treatments such as rituximab (Rituxan®), ofatumumab (Arzerra®), or obinutuzumab (Gazyva®); these drug combinations improve response rate and remission duration. For both fit and less fit older patients who have CLL, ibrutinib (Imbruvica®), given by mouth, is approved for first-line treatment.

The following combinations of drugs have shown the best results in prolonging survival and are approved for first-line treatment.

- Obinutuzumab and chlorambucil
- Ofatumumab and chlorambucil
- Ibrutinib (Imbruvica®), bendamustine and rituximab (BR)
- Ibrutinib (Imbruvica®) and obinutuzumab (Gazyva®)

THE HIGH-RISK CATEGORY: All CLL Patients who have del(17p) or TP53 gene mutations

Young patients and older patients with del(17p) or TP53 mutations do not respond well to any type of chemoimmunotherapy treatment or are likely to have early relapses after first-line therapy. The following treatments are approved for patients with del(17p):

- Ibrutinib (Imbruvica®), given by mouth, is approved for patients who have del(17p) as first-line treatment and is considered the most effective treatment for this category
- Venetoclax (Venclexta™), given by mouth, is approved for patients who have del(17p) and who have received at least one prior therapy.

If these treatments are not appropriate, a clinical trial should be considered. Allogeneic transplant may also be an option in this patient group.

TREATMENT IN A CLINICAL TRIAL

Every new drug or treatment regimen available today has been through a series of studies called “clinical trials” before it became part of standard therapy. Clinical trials are carefully designed and rigorously reviewed by expert clinicians and researchers to ensure as much safety and scientific accuracy as possible. Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, available at **(800) 955-4572**, can offer guidance on how patients can work with their healthcare professional to determine if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct individualized clinical-trial searches for patients, family members and healthcare professionals. When appropriate, personalized clinical-trial navigation by trained nurses is also available through our **Clinical Trial Support Center (CTSC)**. Clinical Trial specialists are registered nurses with expertise in blood cancers. They personally assist patients and caregivers throughout the entire clinical-trial process. For more information, contact an Information Specialist.

For Patients with Relapsed or Refractory CLL

Relapsed CLL is the term for disease that responded to therapy but, after 6 or more months, stopped responding.

Refractory CLL is the term for CLL that does not result in a remission (but may be stable) or disease that gets worse within 6 months of the last treatment.

Patients who are treated for relapsed or refractory CLL often have good quality years of remission after more treatment. Patients should be retested to find out if their mutation profile has changed before planning their next treatment. When symptoms develop, treatments similar to those used initially can be considered.

Drug Therapy

The following drugs can be used to treat relapsed or refractory CLL:

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

Ibrutinib (Imbruvica®) is approved for treatment of relapsed CLL patients. Idelalisib (Zydelig®) is given in combination with rituximab (Rituxan®) and is approved for patients who have received at least one prior form of treatment. Idelalisib is continued indefinitely, as long as there is a good treatment response. Patients who have signs of disease progression while they are taking either of these medications should be maintained on them until a new therapy is added. Some patients can have rapid tumor growth when these agents are stopped without the addition of a new therapy.

Patients with del(17p) do respond to ibrutinib but they may have a higher relapse rate than other patients. Venetoclax (Venclexta™) is approved as a treatment for patients who have CLL with or without del(17p) who have had at least one prior treatment. Duvelisib (Copiktra™) is approved for treatment of relapsed and refractory CLL patients after at least two prior therapies. These patients are advised to speak to their doctors about whether treatment in a clinical trial is a good option for them. Clinical trials involving drug therapies or allogeneic stem cell transplantation can offer more appropriate treatment options.

STEM CELL TRANSPLANTATION

Allogeneic stem cell transplantation is a treatment option for people who have relapsed or refractory high-risk CLL. It may be an appropriate therapy for carefully selected younger patients with CLL who can be matched with a stem cell donor. Talk to your doctor about the best treatment option for you.



GET SUPPORT. REACH OUT TO OUR **INFORMATION SPECIALISTS**

The Leukemia & Lymphoma Society team consists of master's level oncology social workers, nurses and health educators who are available by phone Mon.-Fri., 9 a.m. to 9 p.m. (ET).

Contact us at **800.955.4572** or
www.LLS.org/InformationSpecialists.

Interested in receiving more information?
Text any of these keywords to 411321.

KEYWORD	TOPIC
NEW2CLL	Questions to ask your doctor
CLLCARE	CLL glossary
LIVINGWITHCLL	Cancer-related fatigue
CLLCONNECT	Connect with other patients
CLLSUPPORT	Financial checklist