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# Chronic Lymphocytic Leukaemia (CLL)

**A Guide for  
Patients**

**Leukaemia Care**  
YOUR Blood Cancer Charity

# Introduction

**Being diagnosed with Chronic Lymphocytic Leukaemia (CLL) can be a shock, particularly when you have never heard of it. If you have any questions about CLL, including what causes it, who it affects, how it affects your body, what symptoms to expect and likely treatments - this booklet covers the basics for you.**

The booklet was compiled by Klara Belzar and peer reviewed by Robert Marcus, Professor Chris Fegan and CLL CNS Helen Knight. We are also grateful to Gary Hunter and Steve Colbourne for their valuable contributions as CLL patient reviewers.

For more tailored information, talk to your haematologist, clinical nurse specialist (CNS) or hospital pharmacist.

If you would like any information on the sources used for this booklet, please email [communications@leukaemiacare.org.uk](mailto:communications@leukaemiacare.org.uk) for a list of references.

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# About Leukaemia Care

**Leukaemia Care is a national charity dedicated to ensuring that people affected by blood cancer have access to the right information, advice and support.**

## Our services

### Helpline

Our helpline is available 9.00am - 10.00pm on weekdays and 9.30am - 12.30pm on Saturdays. If you need someone to talk to, call **08088 010 444**

### Nurse service

We have two trained nurses on hand to answer your questions and offer advice and support, whether it be through emailing **nurse@leukaemicare.org.uk**, over the phone on **08088 010 444** or via LiveChat.

### Patient Information Booklets

We have a number of patient information booklets like this available to anyone who has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be found on our

website at **www.leukaemicare.org.uk/resources/filter-by-resource-type/information-booklets**

### Support Groups

Our nationwide support groups are a chance to meet and talk to other people who are going through a similar experience. For more information about a support group local to your area, go to **www.leukaemicare.org.uk/our-support-groups**

### Buddy Support

We offer one-to-one phone support with volunteers who have had blood cancer themselves or been affected by it in some way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call **08088 010 444** or email **care@leukaemicare.org.uk**

### Online Forum

Our online forum, [www.healthunlocked.com/leukaemia-care](http://www.healthunlocked.com/leukaemia-care), is a place for people to ask questions anonymously or to join in the discussion with other people in a similar situation.

### Patient and carer conferences

Our nationwide conferences provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support.

### Website

You can access up-to-date information on our website, [www.leukaemicare.org.uk](http://www.leukaemicare.org.uk), as well as speak to one of our care advisers on our online support service, LiveChat (9am-5pm weekdays).

### Campaigning and Advocacy

Leukaemia Care is involved in campaigning for patient well-being, NHS funding and drug and treatment availability. If you would like an update on any of the work we are currently doing or want to know how to get involved, email [advocacy@leukaemicare.org.uk](mailto:advocacy@leukaemicare.org.uk)

### Journey magazine

Our quarterly magazine includes inspirational patient and carer stories as well as informative articles by medical professionals. To subscribe go to [www.leukaemicare.org.uk/resources/subscribe-to-journey-magazine](http://www.leukaemicare.org.uk/resources/subscribe-to-journey-magazine)

# What is CLL?

**Chronic Lymphocytic Leukaemia (CLL) is a type of blood cancer that occurs when your body makes too many abnormal white blood cells.**

Under normal conditions healthy white blood cells help our bodies fight infection and disease. Leukaemia develops when malignant (cancerous) white blood cells accumulate in the circulating blood and outnumber the normal-functioning cells. As well as in the blood and bone marrow, white blood cells are also found in large numbers in the lymphatic system, the spleen, and in other body tissues. CLL can behave very differently in different people. The term 'chronic' means that in most cases this type of cancer is ongoing and develops, or progresses, slowly (if at all), over months and years, even without treatment. However, in some cases the disease progresses more rapidly and may need early, and possibly more intensive, treatment.

## How blood cells are made?

Blood cells are produced inside

the bone marrow, the sponge-like material found in the centre of the bones. Production of new blood cells is very closely controlled to balance the loss of worn-out cells or cells lost by bleeding or damage. To sustain the necessary levels of blood cells the bone marrow of an adult must produce more than three million blood cells every second. The healthy number of different types of blood cells varies between people but is usually kept within fairly narrow limits.

All mature blood cells originate from immature blood cells called haematopoietic stem cells. In Greek, the word haemato means 'blood' and the word poietic means 'to make'. Less than one in 5,000 bone marrow cells is a stem cell. Haematopoietic stem cells may divide to become a myeloid producing cell (common myeloid progenitor) or a lymphoid producing cell (common lymphoid

progenitor). These immature blood cells go through several stages of development to make the different types of mature blood cells which are then released from the bone marrow into the blood stream where they carry out different functions.

The common myeloid progenitor cell matures into one of three different types of blood cell:

- Red blood cells (erythrocytes) that carry oxygen and other substances to all tissues of the body.
- Platelets (thrombocytes) that form blood clots to stop bleeding.
- Five types of white blood cells (leukocytes): mast cells, basophils, neutrophils, eosinophils and monocytes that form part of the immune system to defend the body against infection and disease.

The lymphoid common progenitor cell matures into another type of white blood cell called a lymphocyte. There are three different types of lymphocyte:

B-lymphocyte (or B-cell) that makes antibodies to help fight infection.

T-lymphocyte (or T-cell) that helps B-lymphocytes make antibodies to help fight infection. They also help kill viruses, fungi and cancer

cells.

Natural killer cell that attacks cancer cells and viruses.

Since CLL is a cancer of the B-lymphocytes, it can also affect the glands of the lymphatic system (lymph nodes), the spleen and other organs. Consequently, affected CLL patients have impaired immune systems and are at greater risk of infections.

When abnormal B-cells accumulate only in the lymph nodes rather than in the blood, the cancer is referred to as small lymphocytic lymphoma (SLL). SLL and CLL are slightly different forms of the same disease, but both conditions respond to the same form of treatment.

## How common is it?

CLL is the most common form of leukaemia in adults in Western countries. Approximately 3,500 adults are diagnosed with CLL each year in the UK alone, which is equivalent to 10 new cases every day. Slightly more men than women tend to be affected by CLL and it is often diagnosed in older people, with 59% of diagnoses made in people aged 70 years and over. For reasons that are not understood, CLL is much more common in white people and less common in Asians. The disease is rarely, if ever, seen in children.

# What causes CLL?

**The exact causes for CLL are unknown, but research is ongoing to find out more. It is not thought to be caused by lifestyle at all, and nothing is known to be able to slow down the progression of CLL.**

In most cases of CLL, DNA damage can be found and there are certain factors that can increase the risk of a person developing CLL:

## Age

The risk of developing CLL increases with increasing age. Only about 10% of CLL patients are younger than 55 years.

## Gender

Men are about twice as likely as women to develop CLL.

## Ethnicity

CLL is more commonly seen in white people (Caucasians) than in any other ethnic group.

## Family history

CLL is between two and seven times more common in close relatives of people who have CLL with 5% of CLL patients having a relative with CLL. Over 20 genes have been identified which predispose people to developing

CLL, however CLL is not considered as a hereditary disease.

## Monoclonal B-cell lymphocytosis (MBL)

MBL is a condition that resembles early CLL but is not malignant and does not require treatment. Approximately 1–2% of MBL patients will develop CLL/SLL each year.

The normal role of a B-lymphocyte is to recognise proteins (so called antigens) on the surface of living structures e.g. viruses, bacteria, foreign or abnormal cells, and produce antibodies to these antigens to try and destroy them. Studies have shown that the antigens CLL cells are recognising could be bacterial in origin or an altered self-protein. At present the data suggests that a normal B-lymphocyte starts to proliferate in response to stimulation by these antigens and then undergoes genetic damage which renders them leukaemic.



# Signs and symptoms

CLL usually develops very slowly and more than half of all patients do not have any symptoms in the early stages of the disease.

In 70-80% of cases, the disease is often found by 'accident' when a person has a routine blood test (full blood count) as part of a health check for something else. As the disease develops, the B-cells grow steadily and accumulate in the bone marrow, the blood and lymph nodes. The overproduction of abnormal B-cells means that the bone marrow may be unable to make enough healthy blood cells as it becomes overcrowded.

Over time CLL patients often develop symptoms as a result of lower than normal numbers of red blood cells (anaemia), white blood cells (neutropenia) and/or platelets (thrombocytopenia).

Some symptoms may occur before you're diagnosed, others you may experience after diagnosis. It's important to know that not everyone will experience the same symptoms.

The most common CLL symptoms may include:

- Feeling tired all the time (fatigue)
- Infections – these may be more frequent, persistent and/or more severe
- Swollen lymph nodes in the neck, armpits or groin
- Breathlessness, tiredness and headaches due to a lack of red blood cells (anaemia)
- Bruising and bleeding easily due to a lack of platelets in the blood (thrombocytopenia)
- Swollen abdomen caused by an enlarged spleen or lymph nodes
- Some abdominal discomfort or unable to eat large meals/ feeling full easily due to enlargement of the spleen
- A high temperature (fever)
- Severe sweating at night
- Weight loss
- Changes in appetite

# Diagnosis

## How is CLL diagnosed?

If CLL is suspected, you'll have a set of tests to confirm the diagnosis. The full blood count (FBC) is one of the key tests in the diagnostic process and is the first step. When a smear of blood is prepared in a laboratory and looked at through a microscope, CLL cells appear as small, dark purple or blue cells, some of which break easily when a microscope film is made - these abnormal cells are known as 'smudge or smear cells' and are a characteristic feature of CLL. A FBC alone and blood cell examination will not be enough to confirm a diagnosis and more specialist blood tests including immunophenotyping will also be needed. The following blood tests and procedures may be used to help confirm diagnosis as well as to enable your consultant to find out about your cancer's stage and plan what treatment you are most likely to benefit from:

## Blood tests

- **Full Blood Count (FBC) and blood cell examination (peripheral blood smear)** - this measures the number and appearance of red cells, white

cells and platelets in the blood. The normal parameters of a full blood count are as follows:

<b>Haemaglobin (Hb) for males</b>	130 - 180
<b>Haemaglobin (Hb) for females</b>	115 - 165
<b>Platelets</b>	150 - 450
<b>White Cell Count (WCC)</b>	4.00 - 11.00
<b>Neutrophils</b>	2.00 - 7.5
<b>Lymphocytes</b>	1.00 - 4.00

- **Immunophenotyping** - this is one of the most important techniques for definitively diagnosing CLL. It involves the use of a machine called a flow cytometer. A flow cytometer emits lasers to detect the type of B-cell that is abnormal by identifying specific markers (prognostic markers) such as CD38 which is found on the outside of CLL cells and where high levels means that the disease is likely to progress quicker.

## Cytogenetic testing

Blood or bone marrow samples may be tested to see if there are any changes in the genes of CLL-cells compared to normal B-cells. Fluorescent in situ hybridisation (FISH) is a very accurate and quick type of cytogenetic test using fluorescent dyes that attach to certain parts of chromosomes.

There are a number of different gene changes specific to CLL cells that can greatly affect the way CLL behaves and how the patient responds to treatment and FISH analysis should always be tested prior to a patient receiving treatment. The two most important genetic prognostic markers for CLL are:

Chromosome 17 deletion 17p (del17p); 1 in 10 CLL patients test positive for del17p.

In addition, more complicated tests to predict prognosis involve directly sequencing the DNA to look for mutations. The most important tests are to identify TP53 mutation or IgVH mutation in your blood.

Del17p and/or TP53 mutations remain the most important adverse prognostic features predicting poorer treatment responses and survival in CLL and should indicate the need to have different therapy to that usually used to treat CLL.

Further testing is not routinely done at diagnosis and only done at a point where disease progression is identified to aid treatment decisions to choose the most appropriate treatment that will have the best response.

## Additional tests

- **Imaging Tests** – ultrasound and CT (computed tomography) scanning enables your consultant to more accurately examine enlarged lymph nodes, liver and spleen before starting treatment.
- **Lymph node biopsy** – You may need a lymph node biopsy if your lymph nodes are swollen. A lymph node biopsy is a minor surgical procedure where a small sample is taken from a lymph node then studied under a microscope. This is usually done in a day and does not require a hospital stay.
- **Bone marrow aspiration and biopsy** – this test is not usually needed to diagnose CLL but may be important to give your consultant information about the extent of CLL cells in your bone marrow before you start any treatment. Also bone marrow tests may be performed after you have completed your treatment to see if the bone marrow disease has completely gone.

# Diagnosis (cont.)

- **Immunoglobulin (antibody)**  
– this test is not used for diagnosis but helps your consultant to check if you have enough antibodies to fight infections and how your body, and more specifically your bone marrow, may respond to treatment.
- **Direct Coombs Test** – in CLL the immune system does not function normally. One consequence of this is that 10-20% of patients develop antibodies which destroy their own red blood cells- so called auto-immune haemolytic anaemia (AIHA)
- **Beta-2 Microglobulin ( $\beta 2M$ ) and Lactate Dehydrogenase (LDH)** – these simple blood tests provide further prognostic information.

## Staging

Staging is a grading method used by consultants to describe the size of the cancer, where it is located and the extent at which the CLL is affecting the blood count and number and size of existing lymph nodes. Grading

CLL helps your doctor predict how quickly the cancer may grow and spread, as well as to decide the best treatment for you and when it should be started.

There are two main systems used to stage CLL. Most doctors in the UK and Europe use the Binet system, whereas in the USA doctors more commonly use the Rai system.

## Binet staging system

This is a three-step staging system (A to C) that is based on the number of groups of swollen lymph nodes and blood cell counts:

### Stage A

- No anaemia and a normal platelet count
- Fewer than three areas of lymph node enlargement

### Stage B

- No anaemia and a normal platelet count and
- Three or more areas of lymph node enlargement

### Stage C

- Anaemia and/or low platelet count
- Regardless of the number of areas of lymph node enlargement

\*The lymphoid areas are the neck, the armpits, the groin, the spleen and the liver (involvement of both groins or both armpits count as one area).

## Rai staging system

This is a five-step staging method (0 to IV) that classifies CLL into low (stage 0), intermediate (stages I and II) and high-risk (III-IV) stages:

### Stage 0

- Absolute lymphocytosis\*
- No enlarged lymph nodes, spleen or liver
- No anaemia, or low platelets

### Stage I

- Absolute lymphocytosis\*
- Enlarged lymph nodes
- No enlarged spleen or liver, anaemia, or low platelets

### Stage II

- Absolute lymphocytosis\*
- Enlarged liver or enlarged spleen
- With or without enlarged lymph nodes

### Stage III

- Absolute lymphocytosis\* and anaemia
- With or without enlarged lymph nodes, spleen or liver

### Stage IV

- Absolute lymphocytosis\* and low platelet count
- With or without enlarged lymph nodes, spleen, liver or anaemia

\*Absolute lymphocytosis means a lymphocyte count higher than 15,000 per cubic millimetre of blood.

# Treatment

**It is generally accepted that CLL is not yet curable, but it is very treatable and it is usually possible to control the disease. Many patients will have a normal life-span with a good quality of life after diagnosis.**

## When to start treatment

If you have no symptoms then you may not need to start treatment straightaway. It will be necessary for you to have regular check-ups and blood tests to monitor whether your disease is progressing. This is often called a 'watch and wait' or 'active monitoring'. It is important you attend these appointments as your consultant will be able to track your condition, talk about how you're feeling and decide on if or when treatment may be needed. Some patients who have Binet stage A CLL may never need treatment.

For more information on Watch and Wait, you can order our booklet by calling the Care Team on **08088 010 444** or emailing [care@leukaemiacare.org.uk](mailto:care@leukaemiacare.org.uk)

The indications to start treatment are:

- Enlarging lymph nodes, liver or spleen
- Falling haemoglobin or platelet counts
- Constitutional symptoms such as fevers, weight loss or night sweats
- The lymphocyte count doubling within a six-month period

A rising white count alone is not usually an indication that treatment is necessary.

The aim of commencing treatment is predominantly to improve patient symptoms and/or improve blood counts and prolong survival with a good quality of life. At present, it is not known whether the use of new combinations of treatment will actually lead to cure but there are hopeful signs this may be the case with some treatments

resulting in survival of 10 years+ with no sign of active CLL in a subset of patients.

## Types of treatment

The types of treatments now available have changed dramatically over the last 20 years. Initially we had only chemotherapy agents but in the late 1990's monoclonal antibodies which target specific proteins on the CLL cell surface became available- so called immunotherapy. Since 2010 a whole new class of therapy has become available - small molecular inhibitors which either target the specific proteins that are keeping the CLL cells alive such as Bruton Tyrosine Kinase, PI-3 Kinase or BCL-2.

The initial studies over the last 20 years involved identifying which were the most effective chemotherapies and then using them in combination. Later the monoclonal antibodies were added to chemotherapy - so called chemoimmunotherapy. Now there are ongoing studies combining all 3 types of treatments, chemotherapy, immunotherapy and small molecular inhibitors.

The standard of first line

treatment for most patients who require treatment for CLL is chemo-immunotherapy. If the CLL cells have a particular abnormality called 17p deletion or TP53 mutation, most forms of chemotherapy will not work very well, or at all and targeted treatment with small molecule inhibitors is usually required.

## Chemotherapy

Chemotherapy is the use of anti-cancer (cytotoxic) drugs to destroy cancer cells. It has a very high success rate in the treatment of CLL. It does not cure the disease but it gives good control for most patients. Chemotherapy will also damage some normal cells as it is toxic to all living cells, which means that there are side effects.

Examples of chemotherapy agents include:

### Purine analogues

Fludarabine and Bendamustine are types of drugs called purine analogue. Purine analogues affect your body's immune system and may reduce your blood counts by affecting the bone marrow's production of normal blood cells. While you are being treated with Fludarabine or Bendamustine, you will be carefully watched for

# Treatment (cont.)

any sign of infection. You may be given drugs to prevent some virus and fungal infections if your lymphocyte count is very low. If this applies to you then you will be given detailed information. Your haematologist or clinical nurse specialist will explain any special precautions you may need to take and will answer all your questions. Fludarabine may cause nausea and/or vomiting but this can usually be controlled by taking drugs called anti-emetics at the same time.

## Alkylating agents

Alkylating agents include cyclophosphamide or Chlorambucil. They are a group of anti-cancer drugs which damage DNA and kill CLL cells. For some patients, who are less fit or who have poor kidney function, alkylating agents may be given alone but most patients have the addition of a monoclonal antibody such as Rituximab, Ofatumumab or Obinutuzumab as the combination works better than Chlorambucil therapy alone.

## Targeted Therapy

Treatments have been developed that target leukaemia cells more precisely than does chemotherapy, which reduces

the effect of treatment on healthy cells and hence side effects. The main types of targeted therapies include:

### Immunotherapy

Immunotherapy is used to 'wake up' your own immune system to fight the cancer. One immunotherapy technique uses monoclonal antibodies to attack and destroy CLL cells. Monoclonal antibodies are drugs that recognise, target and stick to particular proteins on the surface of cancer cells. They can stimulate the body's immune system to destroy these cells. The most common target for immunotherapy is a protein called CD20, which is found on nearly all CLL cells. A drug called rituximab is the most commonly used anti-CD20 treatment. Other more recently available anti-CD20 drugs include Ofatumumab and Obinutuzumab.

### Small molecule Inhibitors

#### B-cell receptor inhibitors

Like normal B-lymphocytes, CLL cells have proteins on the outside called B-cell receptors (BCRs). When a protein binds to a BCR it sends the cell a signal to divide. Unfortunately, CLL cells



are particularly sensitive to BCR signals, which means they divide and produce more CLL cells. One way to stop this is to design a BCR inhibitor, which is a drug which blocks, or inhibits, the BCR signal.

There are two oral (taken by mouth) drugs currently being used which inhibit the BCR pathway:

- Ibrutinib, which blocks a protein called Bruton's Tyrosine Kinase (BTK)
- Idelalisib, which blocks a different protein called phosphatidylinositol 3-kinase (PI3K)

CLL cells are more dependent on these proteins than normal cells so they are vulnerable to Ibrutinib and to idelalisib. Because of the way they work, these drugs are just as effective when a patient has a 17p deletion or a TP53 mutation. This is an important option for patients with TP53 deficient CLL because normal chemotherapy is not successful in this form of the disease and immunotherapy by itself is not very effective.

Both Ibrutinib and Idelalisib interfere with BCR signalling by triggering apoptosis in the

CLL cells. Apoptosis is a natural process in which cells which are worn-out, or no longer needed by the body trigger a 'suicide' pathway. Many anti-cancer drugs work by triggering apoptosis but cancer cells, including CLL cells, find ways to block apoptosis. These two drugs target anti-apoptosis pathways and, despite the name, are designed to switch apoptosis back on. This means that anti-cancer drugs such as Ibrutinib and idelalisib are more able to kill CLL cells at lower doses, which means fewer side effects.

### **BCL-2 inhibitors**

Cancer cells accumulate by switching off the process which enables cells to die- so called apoptosis. CLL cells have a very complex process for switching off apoptosis including high levels of proteins including BCL-2 and MCL-1. Venetoclax is a first in class BCL-2 inhibitor and has been shown to be effective often when other treatments fail and possibly even more effective when used in combination with chemotherapy, immunotherapy and other small molecule inhibitors. So potent is Venetoclax that you may be required to be admitted overnight

# Treatment (cont.)

to start treatment

## **Immunomodulatory drugs**

Also known as IMiDs, immunomodulatory drugs modify, or modulate, the way in which the immune system behaves. They have been widely used for treatment of other forms of blood cancer, and are now being studied for use in treatment of CLL. One of the advantages of IMiDs is that they do not kill all dividing cells, which means that, although they do have side effects, they are not the same as other anti-cancer drugs. This is called non-overlapping toxicity and, for patients, it means better cancer killing without more severe side effects.

## **Chimeric antigen receptor T cells (CAR-T cells)**

Our immune system is able to kill cancer cells. However, to have developed CLL the immune system must have failed. In CAR-T cell therapy a CLL patients own T cells are removed and then manipulated in a laboratory to make them better able to kill CLL cells. They are then infused back

into the patient. At present CAR-T cell therapy is not widely available and just how effective it will be in CLL is still being assessed.

## **Stem cell transplant**

A stem cell transplant involves the use of high-dose treatment to kill as many as possible of the leukaemia cells. This also destroys the bone marrow's ability to make new blood cells, so the patient is given healthy stem cells from a donor. With an allogeneic transplant, there is a chance of life-threatening side-effects because donor cells can attack your healthy tissues in a graft-versus-host effect. This option is therefore only suitable for a small number of patients, with very aggressive disease who are fit enough to be able to tolerate the treatment, because the risks associated with a stem cell transplant aren't justified for patients with a slowly progressing disease like CLL. If this might be an option for you, then your haematologist will discuss it with you and give you a chance to ask questions. However, for most patients the risk of a transplant is

greater than the benefit. There are now many alternatives to stem cell transplantation and the use of this approach is decreasing with the introduction of all the new agents.

### **Radiotherapy**

This treatment uses high-energy rays, usually x-rays, to destroy the cancer cells. Radiotherapy is usually given using a large external machine that directs beams of radiation at the cancer. Most patients with CLL don't get treated with radiotherapy. However, if your spleen or specific groups of lymph nodes are particularly swollen or symptomatic, radiation may help shrink them. The procedure itself is painless, but common side effects of radiation therapy may include redness in the treated area, fatigue, nausea, and vomiting.

### **Splenectomy**

On very rare occasions, selected patients have an operation to remove the spleen (splenectomy). CLL can cause the spleen to become very large, so that it

presses on nearby organs and causes discomfort or pain. Surgery to remove the spleen may be an option if radiotherapy and chemotherapy fail to reduce its size. Your spleen may be removed by keyhole (laparoscopic) surgery or by a cut made just under your ribs in the middle or left side of your abdomen (open surgery). People tend to live a full life without a spleen, however, risk of infection increases. Splenectomy may also be required if the standard treatments for Auto-Immune Haemolytic Anaemia are inadequate.

### **Initial treatment**

If you begin to suffer from symptoms, or if your lymph glands cause problems or the normal blood counts start to fall, you may need to start treatment. The very first treatment you have is called initial, or first-line, treatment.

There are many different first-line treatment options for CLL patients. The choice of treatment will depend on the stage of your disease, your age and general

# Treatment (cont.)

fitness, as well as on whether you carry two prognostic genetic mutations, del17p or TP53. The most common first-line options are:

## **Chemo-immunotherapy**

Fludarabine, cyclophosphamide and rituximab (often abbreviated to FCR). Over 90% of patients respond to FCR treatment with the benefit lasting an average of 5 years but 20% of patients still don't require treatment at 10 years.

Alternative first-line options for patients who cannot have Fludarabine include:

- Bendamustine with rituximab
- Chlorambucil with Obinutuzumab, rituximab or Ofatumumab
- Ibrutinib for elderly patients with co-morbidities
- Clinical trials can also be offered

## **Targeted therapy**

BCR and BCL-2 inhibitors are an initial treatment option for adult patients with a 17p deletion

or TP53 mutation as chemo-immunotherapy is not suitable for this group of patients. Options include:

- Ibrutinib
- Idelalisib in combination with rituximab
- Venetoclax

## **Second-line treatment**

Some patients may be refractory to initial treatment or experience a relapse. Refractory CLL occurs when the cancer has not responded to first-line treatment. A relapse is a return of the disease after a period of time following treatment without any symptoms or sign of the disease. The majority of treatment-responsive patients do eventually relapse. Most patients with relapsed or refractory CLL will need second-line therapy (treatment other than the type used the first time around).

Second-line drug regimens may include:

- FCR
- Bendamustine with rituximab

- Chlorambucil with a monoclonal antibody if the patient only received Chlorambucil on its own as first line therapy.
- Ibrutinib
- Venetoclax
- Idelalisib in combination with rituximab when the disease has been treated but relapsed within 24 months

## Clinical Trials

The transformation in the treatment of CLL seen over the last 20 years has been the result of clinical trials which have compared the standard treatment with what are thought to be the best new treatments.

For example, Fludarabine was commonly used on its own but was shown to be inferior when cyclophosphamide was added to it. Subsequently the combination of Fludarabine, cyclophosphamide and rituximab was shown to be superior to the Fludarabine and cyclophosphamide combination and is presently the gold standard first line therapy for non 17p deleted/mutated patients who are able to tolerate purine analogue therapy.

The present UK first line study in

such patients is the FLAIR study which is comparing FCR with Ibrutinib on its own, Ibrutinib combined with rituximab and Ibrutinib combined with Venetoclax.

For patients not fit enough for Fludarabine based therapy the RIALTO study is comparing Chlorambucil combined with Ofatumumab with Bendamustine combined with Ofatumumab.

# Complications of CLL

## Risk of infection

People with CLL are more vulnerable to infections for a number of reasons:

**Low antibodies** - so called hypogammaglobinaemia which affects up to 20% of patients

**Normal T lymphocyte dysfunction** - the CLL cells themselves switch off the normal T lymphocytes which help prevent viral and fungal infections. Shingles is not uncommon in CLL patients

**Low Neutrophils** - due to marrow infiltration by CLL cells and/or treatment. Neutrophils are a type of white blood cell that play a key role within the immune system fighting infection. If you have a weakened immune system, ordinary infections may occur more often and be more severe or longer lasting or even fatal. Chemotherapy can further weaken your immune system. You will be given detailed advice by your healthcare team on precautions to take to reduce the risk of infection.

Common symptoms of infection include:

- Fever - a temperature of 38 °C or greater
- Aching muscles
- Diarrhoea
- Headaches
- Excessive tiredness

If you develop a fever or any other symptoms that might indicate infection, it is very important that you contact your consultant or specialist nurse immediately as early treatment is necessary.

Ways to reduce the risk of infection:

- **Inoculations** - as soon as you are diagnosed with CLL you should receive vaccinations against the common chest bacteria pneumococcus and haemophilus influenza B and the meningitis causing bacteria meningococcus C. You should also receive the annual flu jab although the majority of patients fail to achieve an adequate immune response to the flu vaccine.

- **Vaccinations to avoid** – patient with CLL should avoid any vaccines which consist of live viruses such as the shingles vaccine.
- **Intravenous immunoglobulin therapy** - if your antibodies are low and you are getting recurrent infections then antibodies can be given as an infusion every 2-4 weeks to reduce the risk of infection.

### Simple ways to help avoid infection:

- Wash your hands regularly.
- Maintain good personal hygiene. Take extra care to keep your mouth clean.
- Avoid people with an infection or any crowded places where there is a risk of infection.
- Avoid foods that may contain harmful bacteria.
- Drink plenty of fluids.

If you would like any more information about how best to avoid infection, talk to your nurse who will be able to offer tailored advice.

For a small number of people, CLL can sometimes change (transform) into a different type of cancer:

Another type of leukaemia called prolymphocytic leukaemia

A faster-growing type of lymphoma called Richter's transformation

When CLL transforms into a type of cancer called diffuse large B-cell lymphoma (DLBCL) it is called Richter's Syndrome. This aggressive type of lymphoma is a serious complication of CLL because it is often much more difficult to treat. Richter's Syndrome affects approximately 2-10% of CLL patients at any time during their disease with similar treatment being given to that used to treat DLBCL.

If your CLL transforms in this way, your consultant will explain what this means in terms of any changes in treatment or outlook.

### Autoimmune haemolytic anaemia

This is a condition in which your immune system does not recognise your red blood cells and destroys them, causing you to become anaemic. 'Autoimmune'

# Complications of CLL (cont.)

refers to the fact that the immune system is damaging your own cells and 'haemolytic' means that the anaemia is occurring because red blood cells are being destroyed. Occasionally, a similar problem may affect platelets, this is called 'autoimmune thrombocytopenic purpura'. 'Thrombocytopenic' means too few platelets (thrombocyte is another name for a platelet) and 'purpura' refers to small purple bruises which may be seen in the skin. Specific therapies will be required for these autoimmune problems usually starting with steroid therapy.

Leukaemia Care offers nationwide support groups for people affected by a diagnosis of a blood or lymphatic cancer. Visit [www.leukaemicare.org.uk](http://www.leukaemicare.org.uk), or call **08088 010 444**, to find out more and to find a group near you.



# Living with CLL

**After a diagnosis of CLL, you may find that it affects you both physically and emotionally. This section will talk about both of these aspects.**

## **Emotional impact of CLL**

Being told you have cancer can be very upsetting. CLL is a rare condition and, because of this, you may need emotional, as well as practical, support. Being diagnosed with a rare disease can affect the whole of you, not just your body, and can impact you emotionally at any point of your 'journey'. It is likely that you will experience a range of complex thoughts and emotions, some of which may feel strange or unfamiliar to you. It is important to know that these feelings are all valid and a normal response to your diagnosis.

Although CLL does not always need treatment, it is a blood cancer and, when treatment is needed, it may be extended over a long period of time. Some patients who are placed on a 'watch and wait' strategy

describe it as 'watch and worry'. It can be stressful if you know you have a blood cancer but you are not having any treatment, and probably not what you were expecting to hear after a cancer diagnosis. You are likely to need a lot of emotional and practical support.

## **Staying active**

One of the most commonly reported symptoms of CLL is fatigue. This isn't normal tiredness and doesn't improve with sleep. The idea of getting out and being active may be the last thing you want to do when you're fatigued, but it is important to try and stay as active as possible as it could make your symptoms less severe.

Some general tips how to deal with fatigue include:

- Have a regular lifestyle – try

# Living with CLL (cont.)

going to bed and waking up approximately the same time every day and try to avoid lying in.

- Take part in regular, gentle exercise to maintain your fitness levels as much as possible.
- Reserve your energy for what you find important and build rest periods around those times.
- Before going to bed avoid stimulants such as alcohol, coffee, tea or chocolate, or using laptops, tablets or mobile phones.
- Keep your bedroom quiet and at a comfortable temperature.
- Talk about your worries with family, friends or your doctor or nurse, or patient support groups.
- Prioritise and pace yourself.
- Take some time between tasks.
- Set realistic goals.
- Discuss your fatigue with your doctor or nurse.

## Practical support

### Work and finances

Being diagnosed with CLL can sometimes lead to difficulties relating to your work life. You may need to ask for special adjustments at work e.g. to help you avoid infections, especially if your job brings you into close contact with people more likely to carry infections. Your diagnosis may lead to temporary sick leave or a reduction in working hours but it can also mean that you have to stop work altogether. You may need to make an arrangement with your employer for times when you may need to go into hospital or for those times when you may not be well enough to go into work.

Your consultant or your GP can arrange letters to confirm your diagnosis and the effects it may have on your work life to your employer. It is often worth taking time to explain CLL to your employer, as it is likely they will never have heard of the disease. It is important for you to know that people with any form of cancer are covered by law by the Equality Act. This means that legally your

employer cannot discriminate against you and must make reasonable arrangements relating to your disease.

Macmillan can give you personal advice over the phone via their helpline on 0808 808 00 00 and you can discuss which benefits you are eligible for. Some Macmillan centres can arrange face-to-face meetings with a benefits advisor. They can also provide financial assistance in the form of grants – ask your nurse in the hospital how to apply.

As CLL is regarded as a cancer, you will also be entitled to apply for a medical exemption certificate which means that you are entitled to free NHS prescriptions. Your GP or specialist nurse at the hospital can provide you with the details how to apply for this. Prescriptions in Northern Ireland are already free.

## Talking about CLL

### Talking to your haematologist

CLL, although the most common form of leukaemia in adults, is still a rare condition. It is

important for you to develop a good working relationship with your haematologist so you are given the best treatment possible for you.

The following gives advice on working well with your haematologist:

- If it's an initial consultation, take along a list of your current medications and doses, and a list of any allergies you may have.
- If you have a complicated medical history, take a list of diagnoses, previous procedures and/or complications.
- Make a list of questions to take to your appointment. This will help the discussion with your haematologist.
- It can be useful to repeat back what you have heard so that you can be sure that you fully understood.
- Note information down to help you remember what was said.
- Be open when you discuss your symptoms and how you are coping. Good patient-doctor communication tends to

# Living with CLL (cont.)

improve outcomes for patients.

Other tips:

- Bring someone along to your appointment. They can provide support, ask questions and take notes.
- Don't be afraid to ask for a second opinion – most haematologists are happy for you to ask.

You need to tell your haematologist if...

You're having any medical treatment or taking any products such as prescribed medicines, over the counter treatments or vitamins. It is important to understand that treatments, including complementary therapies which are perfectly safe for most people, may not be safe if you are being treated for CLL. Remember, if you choose to start any form of complementary therapy outside of your medical treatment, consult your haematology consultant or clinical nurse specialist, prior to beginning it. It is important to understand the difference between complementary therapies, used

alongside standard treatment, and alternative therapies, used instead of standard treatment. There is no evidence that any form of alternative therapy can treat CLL.

## Telling people about your CLL

Telling people you have a rare condition like CLL can be hard to explain. You might find it useful to let your close family and friends, as well as your employer know about your health condition. It might be easier to provide people with basic information and give them information leaflets about CLL if they want to know more in-depth details.

It is probably best to focus conversations on the symptoms that you are experiencing, how the condition affects you and how you feel about it. Often people misunderstand and, unfortunately, it will mostly fall to you to educate them as best as you can. Where possible, it's advisable to let people know what you find helpful and unhelpful, in terms of what others say and do. Often people make assumptions and do what they think helps. For

example, saying you look well, recounting stories of others they know with a similar diagnosis, encouraging you to look ahead and stay positive, which isn't always what people really want to hear. In many ways, the more you communicate with them the better. These points may help you:

- Explain that you have a condition that means your bone marrow does not function properly, and this affects the number of blood cells it produces
- Explain your symptoms (maybe you are tired, or have a lot of pain)
- Explain what you need (maybe more help day-to-day, or someone to talk to)
- Explain that you are more prone to infection and suggest ways that they can help to prevent this (hand washing, not visiting when they have a cold or are ill)

You could also consider the following when telling people about your diagnosis:

- 1. Find out more** - This isn't for everyone, but sometimes trying to find out more about your condition can help you

to cope with your diagnosis and may be of some comfort to you and the people around you. It is important to obtain information from reliable internet sources, charitable organisations or your consultant haematologist. The more you know, the more you can share.

- 2. Have a print-out to hand** - It may help to have a factsheet to hand to share with family and friends. This will take the pressure off you having to remember everything they may want to know.
- 3. Explain your needs** - Try and be clear about what your needs may be. Perhaps you need help with the weekly food shop, help with cooking dinner, or someone to drive you to and from appointments. You may find that friends and family are pleased that they can do something to help you.
- 4. Be open about how you feel** - Don't be afraid of opening up about how you feel, as people who care will want to help you as best they can. Talk as and when you feel comfortable, so those around you will know when you need them most.

# Glossary

## Anaemia

A medical condition in which the red blood cell count or haemoglobin is less than normal.

## B-lymphocyte or B cell

A type of lymphocyte (white blood cell) which produces antibodies to fight infection.

## Bone marrow

The soft blood-forming tissue that fills the cavities of bones and contains fat, immature and mature blood cells, including white blood cells, red blood cells and platelets.

## Chemotherapy

Therapy of cancer using chemicals to stop the growth of cells.

## Clinical trial

A medical research study involving patients with the aim of improving treatments and their side effects.

## Fatigue

Extreme tiredness, which is not alleviated by sleep or rest. Fatigue can be acute and come on suddenly or chronic and persist.

## Full blood count (FBC)

A blood test that counts the number of different blood cells, including white blood cells, red blood cells and platelets.

## Lymph node or lymph gland

An oval shaped organ of the lymphatic system that catches viruses and bacteria. It contains white blood cells that fight infections.

## Spleen

An organ that filters the blood. It removes old blood cells and helps to fight infection. It sits under the ribs on the left of the body.

# Useful contacts and further support

There are a number of helpful sources to support you during your diagnosis, treatment and beyond, including:

- Your haematologist and healthcare team
- Your family and friends
- Your psychologist (ask your haematologist or CNS for a referral)
- Reliable online sources, such as Leukaemia Care
- Charitable organisations

There are a number of organisations, including ourselves, who provide expert advice and information.

## CLLSA

CLL Support Association are a patient-led charity, helping to empower patients and their families through relevant and accurate information.

[www.cllsupport.org.uk](http://www.cllsupport.org.uk)

**0800 977 4396**

## Lymphoma Association

Lymphoma Association offer support and information to patients with lymphoma, including small lymphocytic lymphoma (SLL).

[www.lymphomas.org.uk](http://www.lymphomas.org.uk)

**0808 808 5555**

## Bloodwise

Bloodwise is the leading charity into the research of blood cancers. They offer support to patients, their family and friends through patient services.

**020 7504 2200**

[www.bloodwise.org.uk](http://www.bloodwise.org.uk)

## Cancer Research UK

Cancer Research UK is a leading charity dedicated to cancer research.

**0808 800 4040**

[www.cancerresearchuk.org](http://www.cancerresearchuk.org)

## Macmillan

Macmillan provides free practical, medical and financial support for people facing cancer.

**0808 808 0000**

[www.macmillan.org.uk](http://www.macmillan.org.uk)

## Maggie's Centres

Maggie's offers free practical, emotional and social support to people with cancer and their families and friends.

**0300 123 1801**

[www.maggiescentres.org](http://www.maggiescentres.org)

## Citizens Advice Bureau (CAB)

Offers advice on benefits and financial assistance.

**08444 111 444**

[www.adviceguide.org.uk](http://www.adviceguide.org.uk)

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Leukaemia Care is a national charity dedicated to providing information, advice and support to anyone affected by a blood cancer.

Around 34,000 new cases of blood cancer are diagnosed in the UK each year. We are here to support you, whether you're a patient, carer or family member.

## Want to talk?

Helpline: **08088 010 444**

(free from landlines and all major mobile networks)

Office Line: **01905 755977**

**[www.leukaemicare.org.uk](http://www.leukaemicare.org.uk)**

**[care@leukaemicare.org.uk](mailto:care@leukaemicare.org.uk)**

Leukaemia Care,  
One Birch Court,  
Blackpole East,  
Worcester,  
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Registered charity  
259483 and SC039207

**Leukaemia Care**  
YOUR Blood Cancer Charity

