
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 updated by our Patient Information Writer, Isabelle Leach. The booklet has been peer reviewed by Robert Marcus, Professor Chris Fegan and CLL Clinical Nurse Specialist 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 or hospital pharmacist.

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

In this booklet

Introduction	2
In this booklet	3
About Leukaemia Care	4
What is CLL?	6
Signs and symptoms	10
Diagnosis	12
Treatment	16
Complications of CLL	24
Living with CLL	28
Glossary	38
Useful contacts and further support	39

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 8:30am – 5:00pm Monday - Friday and 7:00pm – 10:00pm on Thursdays and Fridays. If you need someone to talk to, call **08088 010 444**.

Alternatively, you can send a message via WhatsApp on **07500068065** on weekdays 9:00am – 5:00pm.

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** or over the phone on **08088 010 444**.

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/support-and-information/help-and-resources/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/support-and-information/support-for-you/find-a-support-group/**

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 **support@leukaemicare.org.uk**

Online Forum

Our online forum, **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**.

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**

Patient magazine

Our quarterly magazine includes inspirational patient and carer stories as well as informative articles by medical professionals: **www.leukaemicare.org.uk/communication-preferences/**

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 cancerous white blood cells develop in the bone marrow and invade the circulating blood, outnumbering the normal-functioning cells.

In CLL, the white blood cells which become cancerous are the lymphocytes whose function is to recognise bacteria, viruses and toxins, produce antibodies to them and destroy them. 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.

To further understand CLL it is helpful to know about the different types of blood cells and how they are made.

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. 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 have the ability to give rise to myeloid or lymphoid cells which are more specific than stem cells and are called progenitor cells. 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 myeloid progenitor cell matures into one of three different types of blood cell:

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

The lymphoid progenitor cell matures into a type of white

blood cell called a lymphocyte. There are three different types of lymphocyte:

1. B-lymphocytes (or B-cells) make antibodies to help fight infection.
2. T-lymphocytes (or T-cells) destroy the invading organisms that have been tagged by the B-cells as well as cells that have become cancerous.
3. Natural killer cells attack cancer cells and viruses.

CLL is a cancer of the B-lymphocytes, which are also present in the glands of the lymphatic system (lymph nodes), the spleen and other organs. Consequently, 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 CLL?

CLL is the most common form of leukaemia in adults in Western

What is CLL? (cont.)

countries with an incidence of three to five cases per 100,000 persons. Slightly more men than women tend to be affected by CLL and it is often diagnosed in older people, with a median age at diagnosis of between 67 and 72 years. For reasons that are not understood, CLL is much more common in Caucasians 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 factors such as lifestyle, 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 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 Caucasians than in any other ethnic group.
- **Family history** – despite no known cause for CLL, a family history is the most likely and best described risk factor. Family members of CLL patients tend to have a 6% to 9% increased risk for CLL. Over 20 genes have been identified which predispose people to developing CLL; however, CLL is not considered a hereditary disease.
- **Monoclonal B-cell lymphocytosis (MBL)** – MBL is defined as the presence of fewer than $5 \times 10^9/L$ genetically identical B-cells in the peripheral blood and no other signs of disorders in which lymphocytes are produced in excessive quantities. MBL, unlike CLL, does not require treatment. Approximately 1 to 2% of MBL patients will develop CLL/SLL each year.

The normal role of a B-lymphocyte is to recognise 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. At present, the data suggests that normal B-lymphocytes start to proliferate in response to stimulation by antigens and then undergo 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.

CLL is often found by 'accident' when a person has a routine blood test (also known as a full blood count) as part of a health check. As the disease develops, the B-cells grow steadily and accumulate in the bone marrow, 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 diagnosis, while others you may experience them after diagnosis. It's important to know that not everyone will experience the same symptoms.

The most common CLL symptoms may include:

- Fatigue (tiredness and weakness making patients unable to work or perform usual activities)
- 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

If CLL is suspected, you'll have a set of tests to confirm the diagnosis.

Full Blood Count (FBC) and blood cell examination (peripheral blood smear)

The FBC is one of the key tests in the diagnostic process and is the first step. This measures the number and appearance of red cells, white cells and platelets in the blood. When a smear of blood is prepared in a laboratory and looked at through a microscope, CLL cells appear as small, dark purple/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.

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 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.

For patients with CLL, chromosomal analysis has detected several recurrent genetic anomalies that can greatly affect the way CLL behaves and how the patient responds to treatment. Therefore, FISH analysis should always be tested prior to a patient receiving treatment.

One of the most important prognostic markers for CLL is the chromosome 17 deletion 17p (or del17p). 1 in 10 CLL patients

test positive for del17p. In addition, more complicated tests to predict prognosis involve directly sequencing the DNA for mutations. The most important tests are to identify the TP53 mutation or the 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 performed at diagnosis and only done at a point where disease progression is identified to help with treatment decisions and to choose the treatment that will have the best response.

Additional tests include:

- **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 and 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.
- **Immunoglobulin (antibody)**
 - This test is not used for diagnosis but helps your consultant check if you have enough antibodies to fight infections and how your body, and more specifically your bone marrow, may respond to treatment.

Diagnosis (cont.)

- **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. This is called auto-immune haemolytic anaemia (AIHA).
- **2M and LDH** - These simple blood tests provide further prognostic information.

Staging

Staging is a grading method which describes the size of the cancer, where it is located and the extent to 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.

Two staging systems exist to identify the extent of the CLL in patients. In the UK and Europe, the Binet system is used. In the United States, the Rai system is more widely used.

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 the results of the blood test:

Stage A:

- No anaemia (haemoglobin level 10g/dl or more) and a normal platelet count
- Fewer than three areas of lymph node* enlargement

Stage B:

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

Stage C:

- Anaemia (haemoglobin level less than 10g/dl) and/or low platelet count (platelet count less than $100 \times 10^9/L$)
- Unlimited number of areas of lymph node* enlargement

*The areas for lymph nodes are the neck, the armpits, the groin, the spleen and the liver. The involvement of both groins or

both armpits each 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.

Treating CLL

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 '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. For example, 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 Patient Advocacy Team on **08088 010 444**.

The indications to start treatment are:

- Enlarging lymph nodes, liver or spleen
- Falling haemoglobin level or platelet count
- Physical symptoms such as fevers, weight loss or night sweats
- A doubling of the lymphocyte count within a six-month period

A rise in your white cell count alone is not usually an indication that treatment is necessary.

The aim of starting treatment is predominantly to improve the patient's 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 treatment combinations will actually lead to a cure but there are hopeful signs this may be the case with some treatments resulting in survival of

ten years or more with no sign of active CLL in some patients.

Types of treatment

The types of treatment currently available have changed dramatically over the last 20 years. Initially only chemotherapy agents were available but in the late 1990's monoclonal antibodies, which target specific proteins on the CLL cell surface, became available. This is known as immunotherapy. Since 2010, a whole new class of therapy has become available. These consist of small molecular inhibitors which either target the specific proteins that are keeping the CLL cells alive such as Bruton's tyrosine kinase (BTK), phosphatidylinositol 3-kinase (PI3K) and B-cell lymphoma-2 (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 and this combination is called chemoimmunotherapy. Studies of combinations of chemotherapy, immunotherapy and small molecular inhibitors are being conducted.

The standard first line treatment for most patients who require treatment for CLL is chemoimmunotherapy. If the CLL cells have a particular abnormality such as 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 anticancer (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 analogues. 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,

Treating CLL (cont.)

you will be carefully watched for 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 anticancer 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 specifically than chemotherapy,

which reduces the effect of treatment on healthy cells and helps to prevent 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 too many CLL cells. One way to stop this is to use a BCR inhibitor, which is a drug which blocks, or inhibits, the BCR signal.

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

1. Ibrutinib, which blocks the protein BTK
2. Idelalisib, which blocks the protein 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 17p deletion or TP53 mutation. This is an important option for patients with TP53 deficient CLL because normal chemotherapy in these patients 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 by which the body switches on a self-destruct button within damaged or worn

out cells. Many anti-cancer drugs work by triggering apoptosis but cancer cells, including CLL cells, find ways to block the apoptosis process.

BCL-2 inhibitors

CLL cancer cells accumulate by switching off the apoptosis process. CLL cells have a very complex process for switching off apoptosis including high levels of proteins such as BCL-2. Venetoclax is one of the first BCL-2 inhibitors 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.

Immunomodulatory drugs (IMiDs)

IMiDs 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 the 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 anticancer drugs.

Treating CLL (cont.)

Chimeric Antigen Receptor (CAR) T-cells

Normally, 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 patient's own T-cells are removed and genetically modified outside the body so that they recognise the tumour cells. They are then infused back into the patient to attack the cancerous cells. Anti-CD19 CAR-T therapy has shown to be particularly effective for the treatment of CLL patients who experience disease progression on ibrutinib. Although, at present, this treatment is only available to CLL patients as a clinical trial. Your doctor will let you know if you are suitable for this.

Stem cell transplant

A stem cell transplant refers to a transplant of stem cells derived from part of the same individual or a donor. Patients are given high-dose chemotherapy to kill as many leukaemia cells as possible. This also destroys the bone marrow's ability to make new blood cells, so the patient is given healthy stem cells from a donor which is called an

allogeneic transplant. With this procedure, there is a chance of life-threatening side effects because donor cells can attack your healthy tissues in a process called graft-versus-host disease (GVHD). This option is therefore only suitable for a small number of patients, with a very aggressive disease who are fit enough to tolerate the treatment, because the risks associated with a stem cell transplant aren't justified for most 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 transplants and the use of this approach is decreasing with the introduction of all the new agents.

Radiotherapy

Radiotherapy is a treatment that uses high-energy rays, usually x-rays, to destroy the cancer cells. Radiotherapy is usually given using a large external machine that directs large 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 open surgery using a cut made just under your ribs in the middle or left side of your abdomen. People tend to live a full life without a spleen; however, the risk of infection increases. A splenectomy may also be required if the usual treatments for autoimmune haemolytic anaemia are not effective. Autoimmune

haemolytic anaemia, where the immune system destroys the red blood cells, is known to occur in 5% to 10% of patients with CLL, although the reason for this is still unknown.

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

Chemoimmunotherapy

Currently, the first-line treatments for CLL are the combinations of chemotherapies. These are:

- Fludarabine, cyclophosphamide and rituximab (often abbreviated to FCR)

Treating CLL (cont.)

- Bendamustine and rituximab (often abbreviated to BR)

Over 90% of patients respond to FCR treatment; however, it is best given to young (aged 65 years or under), fit patients with previously-untreated CLL, as FCR is an intensive chemoimmunotherapy which carries the potential for more severe side effects.

BR is established as the treatment of choice for elderly patients and patients with kidney disease who cannot tolerate FCR.

Alternative first-line options for more elderly or less fit patients include:

- Chlorambucil with obinutuzumab or ofatumumab
- B-cell receptor inhibitors such as idelalisib or ibrutinib (ibrutinib has shown efficacy in patients with relapsed CLL and as first-line therapy for previously untreated CLL patients with 17p deletion or TP53 mutation)
- Clinical trials with some of the newly developed treatments may be available. These include

cyclin-dependent kinase inhibitors, histone deacetylase inhibitors and chimeric antigen receptor (CAR) T-cell therapy

Targeted therapy

BCR and BCL-2 inhibitors are also initial treatment options for adult patients with a 17p deletion or TP53 mutation as chemoimmunotherapy 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 when a patient initially responds to leukaemia therapy but, after six months or more, response stops. This is also sometimes called a recurrence. 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
- Chlorambucil with a monoclonal antibody (if the patient only received chlorambucil on its own as first line therapy)
- Ibrutinib
- Venetoclax
- Venetoclax with rituximab for patients who have had at least one previous line of treatment
- Idelalisib in combination with rituximab or ofatumumab

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 potentially better new treatments.

For example, clinical trials have shown that the FCR combination was superior to fludarabine and cyclophosphamide, resulting in FCR becoming the standard of care in adult patients with

previously-untreated CLL.

Moreover, trials have shown that FCR is not the best treatment for patients with the chromosomal abnormalities 17p deletion, inactivation of TP53 gene and the unmutated IgHV gene. Ibrutinib, idelalisib and venetoclax have been shown to be effective in patients with 17p deletion or TP53 mutations.

The FLAIR study is comparing FCR with ibrutinib on its own, ibrutinib combined with rituximab and ibrutinib combined with venetoclax. Recruitment of patients started in August 2014 and the trial's estimated end date is June 2020. Approximately 1500 patients will be recruited in total.

For patients not fit enough for fludarabine-based therapy the RIALTO study (NCT01678430) is comparing the combinations of ofatumumab and chlorambucil with ofatumumab and bendamustine. Recruitment of an estimated 670 patients started in December 2011 and the study was completed in April 2018. To date, no final results have been published.

If you would like more information on the clinical trials that might be available to you, speak to your medical team.

Complications of CLL

CLL may cause a number of complications such as those outlined below.

Risk of infection

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

- **Low antibodies** – This is known as hypogammaglobinaemia and affects more than 25% of patients.
- **Normal T-lymphocyte dysfunction** – The CLL cells switch off the normal T-lymphocytes whose function is to 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 by helping fight infection. If you have a weakened immune system, ordinary infections may occur more often, be more severe, last longer or even be 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 clinical nurse specialist 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** - You should not have immunisations with live vaccines as it is expected to reduce the response to vaccination. In the UK, live vaccines include rubella, mumps, measles (MMR), BCG, yellow fever and shingles vaccines. In addition, your treatment can lower the body's resistance to infection and there is a chance that you may get the infection the immunisation is meant to prevent.
- **Intravenous immunoglobulin (IVIg) therapy** - If your antibodies are low and you are getting recurrent infections then antibodies can be given as an infusion every two to four 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.

Disease transformation

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

- Another type of leukaemia called prolymphocytic leukaemia

Complications of CLL (cont.)

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

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' 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, 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 and management of a CLL diagnosis

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 you as a whole, 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. These may include uncertainty, isolation, anxiety, anger, sadness and depression, fears of recurrence and difficulties in planning for the future. 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, as it was probably not what you were expecting to hear after a cancer diagnosis. Being fearful of the unknown, especially when we are feeling threatened, is natural. You may experience an increased heart rate, rapid breathing, and muscle tension. This 'fight or flight' response is completely natural and helps us to face a danger or run away. Talk to your doctor and clinical nurse specialist about any anxiety.

You may also react by feeling angry at the cancer diagnosis, yourself, the healthcare team or family and friends. This is again a natural response felt by many patients. Understanding exactly what is making you angry will

help you deal with your feelings effectively. Setting yourself achievable but demanding goals will help reduce the anger and impatience, especially with each passing success.

Don't forget to congratulate yourself for each successfully completed task, however small. Physical exercise is a great way to release your anger and frustrations, and channel energy positively with no negative impact on the body.

These responses will ease over time with the building of daily routines and planning things for the future, which will help you to cope with the physical effects of anxiety and anger. Cognitive behavioural therapy can help you deal with your worrying thoughts.

Understanding each emotion and developing ways that help you deal with them will help you move forward with your life. Once you have a clear path set out in front of you, you will be able to develop a clearer picture of where you are headed. Gaining a sensible balance between being vigilant about your symptoms and carrying on with your life will help

ease any anxieties.

You may also find yourself feeling low, which is a natural effect of your situation and the illness, treatment and recovery process. However, if this low mood persists for more than several weeks, and you feel hopeless, and lose interest and pleasure with things in life, then you may have depression. Your first steps should be to speak to your loved ones about your mood and state of mind, and then contact your GP.

You may lift the way you feel by engaging in activities that you were enjoying before the diagnosis and connecting back with your life. Only do as much as you can and try and talk about your thoughts and feelings. This will help lighten your burden and put things into perspective.

Staying active

One of the most commonly reported symptoms of CLL is fatigue. This is not normal tiredness and does not improve with sleep. Fatigue is a tiredness and weakness that makes you unable to work or perform usual activities. The idea of getting out and being active may be the last

Living with CLL (cont.)

thing you want to do when you are experiencing fatigue, but it is important to try and stay as active as possible as it could help with your symptoms. Discuss your fatigue with your doctor or nurse.

Some general tips on how to deal with fatigue include:

- Have a regular lifestyle – try 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. Set yourself realistic goals and take some time between tasks.
- 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.
- Prioritise and pace yourself. You can gradually build your self-

confidence and self esteem by engaging in the activities you did before the diagnosis, and socialising with family, friends, and those in a similar position to you.

Simple practices based on mindfulness and relaxation techniques can help you calm the mind, release tension and ease any pain.

- Put yourself in a relaxing environment, sitting or lying down comfortably.
- Loosen your clothing so you can move more freely.
- Calmly breathe in through your nose, and out through your mouth, developing a steady natural rhythm, focusing on your chest and abdomen as you do so.
- Visualise that you are inhaling positivity and exhaling negativity.

Taking time out of your day to do these exercises will help quieten your mind and remove the stress of coming to terms with your diagnosis, making you feel calmer and more relaxed.

Talking about CLL

Talking to your haematologist and healthcare team

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 and healthcare team so you receive the best treatment possible.

The following gives advice on working well with your haematologist and healthcare team:

- At your 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.

Examples of questions to ask the doctor are:

- What tests will be needed?
- What will the tests show?

- How long will it take to get the results back?
- How common is this condition?
- What sort of treatment will be needed?
- How long will the treatment last?
- How will I know if the treatment has worked?
- What will the side effects be?
- Will any intensive treatment or palliative care be needed?
- Are there any foods or medications that need to be avoided?
- Will I be able to go back to work?
- Where can I get help with claiming benefits and grants?
- Where can I get help dealing with my feelings?

It can be useful to repeat back what you have heard so that you can be sure that you fully understood or even write it down during the appointment.

Be open when you discuss your symptoms and how you are coping. Good patient doctor

Living with CLL (cont.)

communication tends to improve outcomes for patients.

Other tips include:

- 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.

Talking to family and friends about your CLL

Telling people that 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 or booklets about CLL like this one 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 and encouraging you to look ahead and stay positive 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 (regular hand washing and not visiting when they have a cold or are ill)

When telling people about your diagnosis, using a conciliatory tone will help keep both yourself and the other person calm. Deliver what you have to say slowly,

calmly, concisely, and sentence by sentence to allow the other person time to take in the information. Be sincere, and hold their hands if you need to.

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 or this booklet 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

Living with CLL (cont.)

from appointments. You may find that friends and family are pleased that they can do something to help you. Sometimes people feel guilty if they get cancer, that it's their fault, and that they will be a burden on those around them. This is where your loved ones come in, so make sure you do ask for and accept offers to help and support you. Do not try to cope on your own. If they offer to help, tell them that you will get in touch when you need them.

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. Talk about your worries with family, friends or patient support groups. Let people know what you do and don't want to do, how you do and don't wish to be treated, and what you do and don't feel comfortable talking about. Sometimes, it is difficult for your family, friends and colleagues to understand what you are feeling and going through. Being clear

will help create the kind of positive, supportive, and caring environment that will help as you move forward with your life.

Repeating yourself to different people can become burdensome. Your network of family and friends can help you out by telling those beyond them about your current situation. You can receive help from us on how to deal with telling your family and friends. You can visit www.leukaemiacare.org.uk, or call **08088 010 444**, to find out more.

Work arrangements

Being diagnosed with CLL can sometimes lead to difficulties relating to your work life. You may need to ask for special adjustments at work, for example, 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 legally by the Equality Act. This means that your employer cannot discriminate against you and must make reasonable arrangements relating to your disease.

Financial help

You can speak to our Patient Advocacy team on **08088 010 444** who can provide you with general advice about what benefits you may be entitled to. If you would like more personal advice, Macmillan can offer this via their helpline on **0808 808 00 00**. 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 clinical nurse specialist at the hospital can provide you with the details on how to apply for this. Prescriptions in Northern Ireland are already free.

Survivorship

Survivorship is a term to describe someone who is living with or beyond a cancer diagnosis.

Survivorship can be defined as: "...cover[ing] the physical, psychosocial and economic issues of cancer, from diagnosis until the end of life. It focuses on the health and life of a person with cancer beyond the diagnosis and treatment phases. Survivorship includes issues related to the ability to get health care and follow-up treatment, late effects of treatment, secondary cancers and quality of life. Family members, friends and caregivers are also part of the survivorship experience."

When living with cancer, you will face new challenges to cope with from physical to psychological and social ones. Survivorship aims to provide personalised care based on improving your health, wellbeing, quality of life, and your confidence and motivation, to

Living with CLL (cont.)

help you manage. Survivorship also focuses on your health and life with cancer after the end of treatment until the end of life.

Palliative care

Palliative care, also known as supportive care, involves a holistic or "whole person" approach, which includes the management of pain and symptoms, as well as psychological, social and spiritual support for you and your loved ones.

Palliative care aims to reduce the symptoms, control the CLL, extend survival, and give you and your loved ones the best quality of life possible. Your doctor will discuss the options with you in detail before you decide the next steps. Palliative care will be provided by a team of health and social care professionals trained in palliative medicine who will coordinate the care. These professionals can include your GP, hospital doctors and nurses, community nurses, hospice staff and counsellors, social care staff, physiotherapists, occupational therapists, complementary therapists, and religious leaders, if you would like this. The palliative care services

may be provided by the NHS, local council or a charity. You may receive day-to-day care at your home and at the hospital.

End of life care

If the various treatment options have not worked and you are going through palliative care, end of life care may be offered. End of life care begins when it is needed and may last a few days, months or years.

End of life care is support for people who are in the last few months or years of their life. The aim is to help patients enjoy a good quality of life until they die, and to die with dignity. The professionals looking after you will ask about your wishes and preferences on how to be cared for and put these into action. They will also provide support to your family, carers and loved ones. You will be able to decide where you will receive end of life care, be it at home or in a care home, hospice or hospital. The same will be true of where you would like to die. Wherever this is, you will receive high quality end of life care.



Glossary

Anaemia

The condition where the number of red blood cells are reduced. Red blood cells contain haemoglobin and transport oxygen to body cells. This may be due to a lack of iron, leukaemia, or sickle cell disease.

Antigen

A toxin or other foreign substance which induces an immune response in the body, especially the production of antibodies.

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

A group of drugs that work in different ways to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing.

Clinical trial

A medical research study in which healthy volunteers or patients

receive drugs to establish their efficacy and safety with the aim of improving treatments and their side effects.

Clonal

This describes a group of cells or organisms that are descended from and genetically identical to a single cell.

Fatigue

Tiredness and weakness rendering the patient unable to work or perform usual activities.

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

Components of the lymphatic system (part of the body's immune system) that contain lymphocytes which produce antibodies and macrophages to digest dead cells.

Spleen

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

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

0800 977 4396

Lymphoma Association

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

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

Cancer Research UK

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

0808 800 4040

www.cancerresearchuk.org

Macmillan

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

0808 808 0000

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

Citizens Advice Bureau (CAB)

Offers advice on benefits and financial assistance.

08444 111 444

www.adviceguide.org.uk

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

care@leukaemicare.org.uk

Leukaemia Care,
One Birch Court,
Blackpole East,
Worcester,
WR3 8SG

Registered charity
259483 and SC039207

Leukaemia Care
YOUR Blood Cancer Charity