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Chronic Lymphocytic Leukaemia (CLL)

A **Guide for Patients** in New Zealand

October 2020

Acknowledgements

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Adaptation of the booklet for New Zealand conditions has been undertaken by Gillian Corbett MBChB, FRACPath, MRCP, FRACP, haematologist and Trustee, CLL Advocates NZ, Neil Graham FRACP, FRCP, Executive Director, CLL Advocates NZ, and Catherine Isaac, Trustee, CLL Advocates NZ.

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Contents

Introduction

Being diagnosed with Chronic Lymphocytic Leukaemia (CLL) can be a shock, particularly if 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.

As a CLL patient advocacy group, we aim to improve survival and quality of life for New Zealanders living with CLL. At the same time, through education, research and knowledge sharing, we seek to empower patients to advocate for and access equitable, world-class treatment. We hope this booklet will help advance that objective.

If we can help you with any other information, visit our website clladvocates.nz or email us at info@clladvocates.nz.

For more tailored information, talk to your haematologist or clinical nurse specialist.

1 What is Chronic Lymphocytic Leukaemia (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, eventually outnumbering the normal-functioning cells.

In CLL, the white blood cells which become cancerous are called lymphocytes. Their function is to recognise bacteria, viruses and toxins, produce antibodies to them, and destroy them. As well as being 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 treatment.

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

I. How blood cells are made

Blood cells are produced inside the bone marrow, the soft 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 and cells lost by bleeding or damage. The healthy number of different types of blood cells varies among people but is usually kept within a fairly narrow range.

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'). Fewer 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.

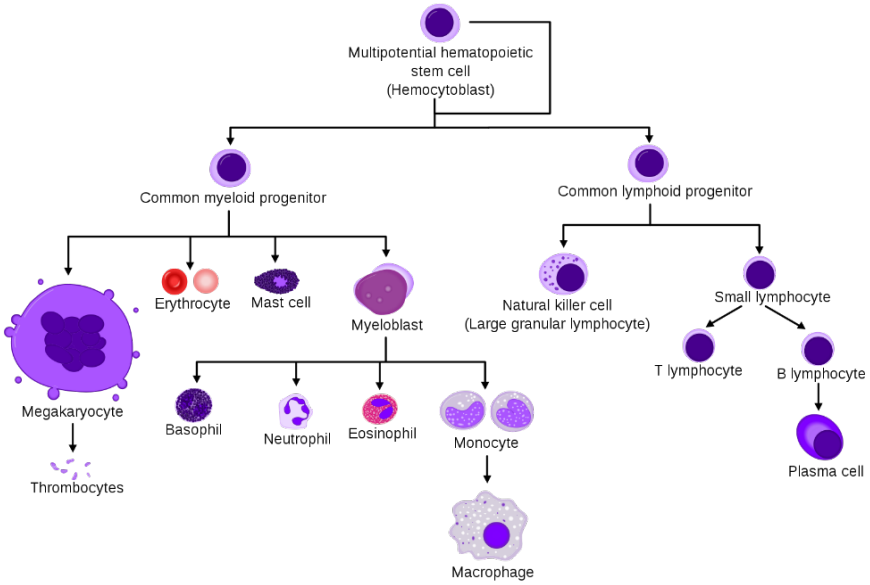


Diagram showing the development of different blood cells from hematopoietic stem cells to mature cells.

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

- **Red blood cells (erythrocytes)** carry oxygen and other substances to all tissues of the body.
- **Platelets (thrombocytes)** form blood clots to stop bleeding.
- 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:

- **B-lymphocytes (or B-cells)** make antibodies to help fight infection.

- **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.
- **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.

II. How common is CLL?

CLL is the most common form of leukaemia in adults in Western countries, with an incidence of three to five cases per 100,000 persons. Approximately 234 adults are diagnosed with CLL each year in New Zealand (MoH data from 2004 - 2015, range 190 - 309), which is equivalent to 5 new cases every week. At any one point there are over 2,000 people living with CLL in the NZ population. 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 more common in Caucasians and less common in Asians. The disease is rarely, if ever, seen in children.

CLL can be asymptomatic, so not diagnosed. The disease is therefore recognised to be more common than the incidence derived from data of diagnosed cases.

III. What causes CLL?

The exact causes for CLL are unknown, and research to find out more is ongoing. It is not thought to be caused by factors such as lifestyle.

In most cases of CLL, DNA damage can be found in the lymphocytes. 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 suggest that normal B-lymphocytes undergo genetic damage which renders them leukaemic.

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 more likely than 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 $5x10^9$/L (about the normal range) of clonal 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.

2 Signs and Symptoms of CLL

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 other symptoms may be experienced after diagnosis. It's important to know that not everyone will experience the same symptoms. It's also important o note that not everyone will experience symptoms of any sort, and it is not uncommon for the disease to be stable and not progress for many years, if at all.

The most common CLL symptoms 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 being 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

3 Diagnosis

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

I. Common tests

a. 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. The normal parameters of a full blood count are as follows:

Haemoglobin (Hb) for males	130 – 175
Haemoglobin (Hb) for females	115 – 155
Platelets	150 – 400
White Cell Count (WCC)	4.00 – 11.00
Neutrophils	1.90 – 7.5
Lymphocytes	1.00 – 4.00

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. However an 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.

b. Immunophenotyping

This is the most important technique 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 proteins on the surface of the lymphocytes which are diagnostic of CLL.

c. 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 undertaken 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. Del17p and/or TP53 mutations remain the most important adverse prognostic features predicting poorer treatment responses and survival in CLL, and could indicate the need to have different, more tailored therapy than that routinely used to treat CLL.

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 and the IgVH mutation in your blood. Testing is not available in New Zealand at present for IgVH.

Further testing is not routinely performed at diagnosis and only done at a point where disease progression is identified, in order to

help with treatment decisions and to choose the treatment that will have the best response.

Additional tests include:

i. Imaging tests

Ultrasound and CT (computed tomography) scanning can be used to examine enlarged lymph nodes, liver and spleen before starting treatment.

ii. Lymph node biopsy

You may need a lymph node biopsy if your lymph nodes are swollen. This 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.

iii. 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.

iv. 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. The three main antibodies relevant to CLL are IgG, IgA and IgM.

v. Direct Coombs Test

In CLL the immune system does not function normally. One consequence of this is that 5 -10% of patients can develop antibodies which destroy their own red blood cells, called auto-immune haemolytic anaemia (AIHA). This can be diagnosed by

the Direct Coombs test. There are, however, other causes of anaemia in CLL.

II. Staging

Staging is a grading method which describes the extent of CLL, 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 rapidly 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.

a. 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	Status of anaemia	# swollen lymph nodes
Stage A	No anaemia (haemaglobin level 100g/l or more) and a normal platelet count	Fewer than three areas of lymph node group enlargement
Stage B	No anaemia and a normal platelet count	Three or more areas of lymph node group enlargement
Stage C	Anaemia (haemaglobin level less than 10g/dl) and/or low platelet count (platelet count less than 100x109/L)	Multiple areas of lymph node group enlargement

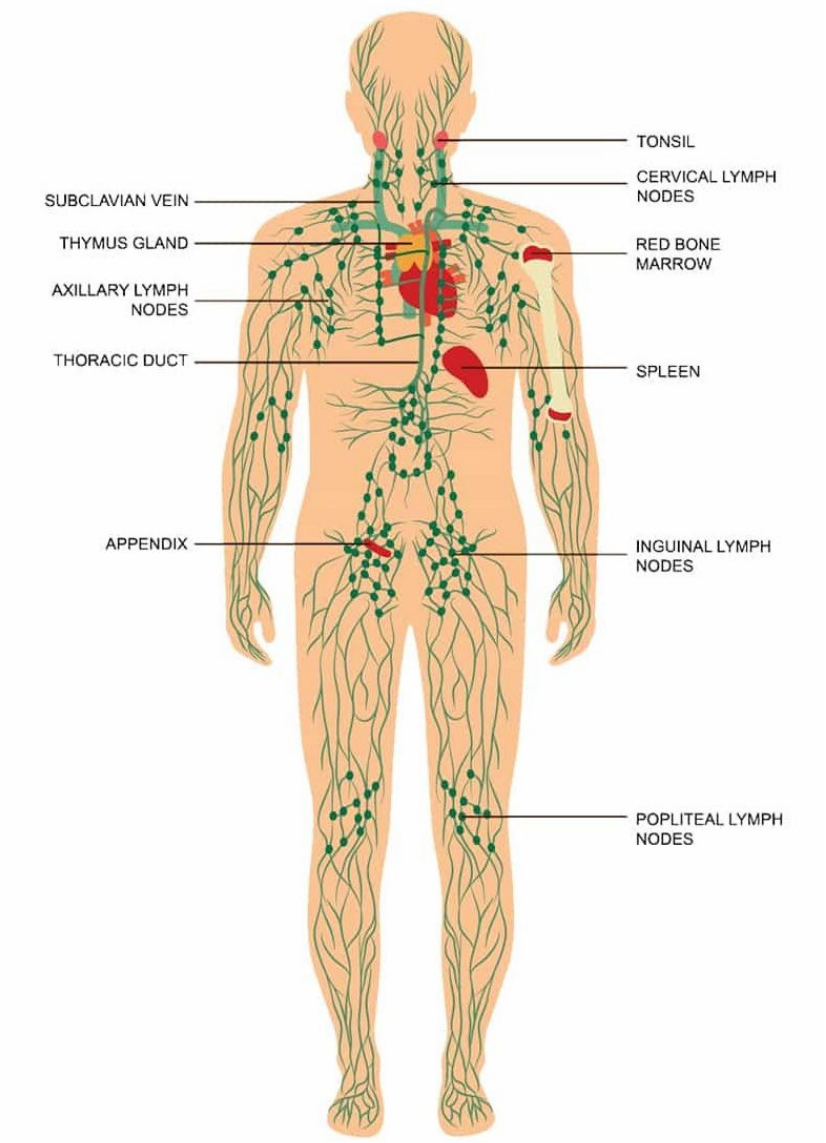
b. Rai staging system

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	CLL risk level	Extent of effect
Stage 0	Low	Increased lymphocytes in the blood or bone marrow (lymphocytosis)
Stage I	Intermediate	Lymphocytosis and enlarged lymph nodes
Stage II	Intermediate	Lymphocytosis, enlarged liver or spleen, and/or enlarged lymph nodes
Stage III	High	Lymphocytosis and other features of Stage II, and anaemia
Stage IV	High	Lymphocytosis and other features of Stage III, and reduced platelets (Thrombocytopenia)

The main areas for lymph nodes are the neck, the armpits, the groin, the spleen and the liver. The involvement of both groins or both armpits count as one area. Lymph nodes are an important part of the immune system.

Below is a diagram of the body's lymphatic system.



The lymphatic system of the human body

4 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 near-normal life-span with a good quality of life after diagnosis.

If you have no symptoms, you may not need to start treatment straightaway. If this is the case for you, you will need 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 with you about how you're feeling, and decide if or when treatment may be needed. Some patients who have Binet stage A CLL may never need treatment, as their disease may not progress.

'Watch and wait' can be associated with a significant stress response, but there is no evidence that this approach has any adverse CLL outcomes in comparison to treating people in this group earlier. You should feel free to ask your haematologist to explain clearly to you the basis for adopting a 'watch and wait' approach, if that is what has been recommended in your case.

Similarly, you should also feel able to ask your haematologist or GP about any aspects of your CLL that you are worried about, or don't understand. See page 35 "Talking about CLL", which gives some examples of issues.

I. When to start treatment

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 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 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.

II. 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 1990s monoclonal antibodies became available, that target specific proteins on the CLL cell surface. This is known as immunotherapy. Since 2010, a whole new class of therapy has become available. These consist of small molecular inhibitors which 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).

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 chemo-immunotherapy. Studies of combinations of chemotherapy, immunotherapy and small molecular inhibitors are continuing.

The standard first-line treatment for most patients who require treatment for CLL is chemo-immunotherapy. 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 the best option.

a. Chemotherapy

Chemotherapy is the use of anticancer (cytotoxic) drugs to destroy cancer cells. It has a very high response rate in the treatment of CLL. It does not usually cure the disease but it gives good control for most patients, especially those with IgVH mutated disease. 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:

i. 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*, you will be carefully watched for any sign of infection. You may be given drugs to prevent infections if your lymphocyte count is very low. If this applies to you, 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.

ii. 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.

b. Targeted therapy

Treatments have been developed that target leukaemia cells more specifically than chemotherapy, and which reduce the effect of treatment on healthy cells and help prevent side effects. The main types of targeted therapies include:

i. 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. *Rituximab* is the most commonly used anti-CD20 treatment. Other more recently available anti-CD20 drugs include *ofatumumab* and *obinutuzumab*.

ii. Small Molecule Inhibitors

- B-cell receptor inhibitors

Like normal B-lymphocytes, CLL cells have proteins on the outside of their cell called B-cell receptors (BCRs). When a protein binds to a BCR, it sends the cell a signal to proliferate. They also prolong the survival of the CLL cells. Unfortunately, CLL cells are particularly sensitive to BCR signals, which means they divide and produce too many CLL cells. One way to stop these processes is to use a BCR inhibitor (BCRI), which is a drug that blocks, or inhibits, the BCR signal,interfering with the activation, growth and survival of CLL cells, and triggering apoptosis. 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 some cancer cells, including CLL cells, find ways to block the apoptosis process.

The two oral (taken by mouth) drugs currently available to inhibit the BCR pathway are *ibrutinib*, which blocks the protein BTK and *idelalisib,* which blocks the protein PI3K.

- *Ibrutinib*

  CLL cells are more dependent on the above proteins than normal cells so they are vulnerable to *ibrutinib,* which interferes with BCR signalling in the CLL cells and triggers apoptosis. Because of the way it works, *ibrutinib* is just as effective when a patient has 17p deletion,TP53 mutation and IgVH mutation. It is an important option for patients with TP53 deficient CLL, because normal chemotherapy in these patients and immunotherapy by itself or in combination with chemotherapy are not usually effective.

  Unfortunately, *ibrutinib* is not available as a funded medication in NZ currently (October 2020). If you need to access this treatment, you will either need to raise the money to pay for it, have it provided on compassionate grounds, or get it as part of a drug trial. There are two drugs closely related to ibrutinib that are currently in development, *zanubrutinib* and *acalabrutinib*. These are only available in NZ in clinical trials.

- *Idelalisib*

  This drug also interferes with BCR signalling by triggering apoptosis in the CLL cells. Idelalisib is given as a regular/continuous oral medication, usually in conjunction with rituximab. It has been used as initial treatment, and, more commonly, in relapsed disease including pre-treated patients. It

has a high response rate (>90%) in CLL, but also has a high side effect profile, resulting in much reduced use in recent times. It is hoped that second generation related medications may have fewer side effects. It is not funded in NZ.

– BCL-2 inhibitors

The process whereby CLL cells switch off apoptosis, thus allowing them to accumulate, is very complex, and includes producing high levels of proteins such as BCL-2.

- *Venetoclax*

  This 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.

  Funding for *venetoclax* in New Zealand was approved late in 2019. It is funded, in combination with *rituximab,* for the treatment of CLL that has relapsed within 36 months of previous treatment, and as monotherapy for the treatment of previously untreated CLL with 17p deletion or TP53 mutation. Treatment with *venetoclax* may require the patient to be admitted to hospital overnight in the early stages of treatment if their lymphocyte count is high. This is due to CLL cell destruction which can be severe and life-threatening (Tumour Lysis Syndrome).

c. Corticosteroids

Corticosteroids such as prednisone may be used in specific CLL complications, for example, auto-immune haemolytic anaemia.

d. 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*. At present CAR T-cell therapy is only available to CLL patients as a clinical trial, as it is in the early stages of development for CLL treatment. Your doctor will let you know if this treatment may be suitable and available for you.

e. Stem cell transplant

An allogenic stem cell transplant refers to a transplant of stem cells derived from a donor (who may be related or unrelated, for example from a donor bank). Previously, a CLL patient's own stem cells have sometimes been used (called an autologous transplant) but this is currently not being done.

Patients undergoing an allogenic transplant 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. The patient is then given healthy stem cells from a donor. 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). Because of these risks a stem cell transplant is only suitable for a small number of patients who have very aggressive disease and who are fit enough to tolerate the treatment. If this might be an option for you, your haematologist will discuss it with you. 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 has accordingly decreased in recent years.

f. 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 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.

g. Splenectomy

A splenectomy is an operation to remove the spleen. In some patients 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 are generally able 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 auto-immune haemolytic anaemia are not effective. Auto-immune haemolytic anaemia, where the immune system destroys the red blood cells, is known to occur in 5 to 10% of patients with CLL (see page 31).

III. Treatment pathways

a. Initial (first-line) treatment

There are various 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:

i. Chemo-immunotherapy

Current first-line treatments for CLL are combinations of chemotherapies. These are:

- *fludarabine*, *cyclophosphamide* and *rituximab* (often abbreviated to *FCR*)
- *bendamustine* and *rituximab* (often abbreviated to *BR*)

Over 90% of patients respond to *FCR* treatment; however, it is best given to fit young (aged 70 years or under) patients with previously-untreated CLL, as *FCR* is an intensive chemo-immunotherapy which carries the potential for more severe side effects.

BR is established as the treatment of choice for fit older patients who are unlikely to tolerate *FCR*.

ii. Alternative first-line options for more elderly or less fit patients

- *chlorambucil* with *obinutuzumab* or *ofatumumab*

For elderly or less fit patients, who are less likely to respond to chemo-immunotherapy, and advanced, recurrent, poor prognostic groups such as 17p deletion, BCR and BCL-2 inhibitors are also first-line treatment options. Options are:

- *ibrutinib*
- *idelalisib* in combination with *rituximab*
- *venetoclax*

iii. Clinical trials

Trials with some of the newly developed treatments that may be available include cyclin-dependent kinase inhibitors, histone deacetylase inhibitors, chimeric antigen receptor (CAR) T-cell therapy, and second generation BCR and BCL-2.

b. Second-line treatment

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 months or years, response stops. This is 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 i.e. treatment other than the type used at first-line.

Second-line treatment regimens may include:

- *FCR*
- *chlorambucil* with *rituximab*
- *ibrutinib*
- *venetoclax*
- *venetoclax* with *rituximab* for patients who have had at least one previous line of treatment
- *iodelalisib* in combination with *rituximab*

c. 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* only. As a

result, *FCR* became the standard of care for many patients with previously-untreated CLL.

However, trials have also 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*, *venetoclax* and *idelalisib* have been shown to be effective in patients with 17p deletion or TP53 mutation.

A six-year UK first-line study (FLAIR) of approximately1500 patients comparing *FCR* with *ibrutinib* on its own, *ibrutinib* combined with *rituximab*, and *ibrutinib* combined with *venetoclax* is due to be completed in 2020.

For patients not fit enough for *fludarabine*-based therapy the RIALTO study (NCT01678430) compared 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.

You can get details of clinical trials available in New Zealand through the app on our website at https://clladvocates.nz/resources/clinical-trials/

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

5 Complications of CLL

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

I. Risk of infection

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

a. Low antibodies

This is known as hypogammaglobinaemia and affects more than 25% of patients.

b. Normal T-lymphocyte dysfunction

The CLL cells switch off the normal T-lymphocytes, whose function is to help prevent viral and fungal infections. One example of the consequence is that shingles is not uncommon in CLL patients.

c. Low neutrophils

This is 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.

d. Treatment

Chemotherapy can further weaken your immune system, for example, FCR can lower the body's resistance to infection and also increase the risk of infection.

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 38ºC or greater
- Aching muscles
- Diarrhoea
- Headaches
- Excessive tiredness
- Productive cough/sore throat

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

e. Ways to reduce the risk of infection

i. Inoculations

You should receive an annual flu vaccine, and consider vaccinations against the common chest bacteria, pneumococcus and Haemophilus influenzae B, and the meningitis-causing bacteria meningococcus C.

ii. Vaccinations to avoid

You should not have immunisations with live vaccines as they can result in overwhelming infection. Live vaccines include rubella, mumps, measles (MMR), BCG, yellow fever and shingles vaccines. Vaccine response in CLL patients is often blunted.

iii. Intravenous immunoglobulin therapy

If your antibodies are low and you are getting recurrent infections then antibodies can be given as an infusion every four to six weeks to reduce the risk of infection.

iv. Taking extra care

- 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 or doctor who will be able to offer tailored advice.

II. Disease transformation and risk of other cancers / disorders

a. Richter's Transformation

For some people, CLL can change (transform) into a different type of cancer, including a faster-growing type of lymphoma called diffuse large B-cell lymphoma (DLBCL). This aggressive type of lymphoma is a serious complication of CLL because it is often much more difficult to treat. When CLL transforms into DLBCL, this is called Richter's Transformation (also called Richter's Syndrome). It affects approximately 2-10% of CLL patients at any time during their disease and requires similar treatment being given to that used to treat non-CLL DLBCL.

b. Risk of skin cancers

People with CLL are at greater risk of developing other cancers, in particular, skin cancers.

New Zealand already has one of the highest rates of skin cancers in the world, most commonly due to over-exposure to the sun. CLL patients are at higher risk of developing basal cell carcinoma and squamous cell carcinoma, and less commonly, melanoma, the most dangerous form of skin cancer. These cancers are also often more aggressive in CLL patients.

The most likely cause of the increased rate and invasiveness of skin cancers in CLL patients is their suppressed immune surveillance systems. In people with healthy immune systems, early skin cancers are usually detected and suppressed or destroyed before they become a problem. But in CLL patients, and people over 70 generally, loss of this control system increases the rate at which cancer cells can grow and spread.

While the risk of melanoma among CLL patients is smaller than the risk of basal cell and squamous cell cancers, it is the skin cancer most likely to cause death. A 2018 study and full analysis of detection rates and treatments of melanoma by the University of Rochester Medical Cancer and Wilmot Cancer Center found that people with CLL have a 600% higher risk of developing melanoma.

You should inform your specialist if you have any type of skin cancer at the time of diagnosis of CLL. Thorough dermatologic examination should be undertaken at the time of diagnosis and frequently thereafter, to help ensure any skin cancer is detected and treated early.

It is also important to protect yourself from over-exposure to the sun and ensure you are well informed on what to look for in regularly self-checking your skin.

c. Risk of other second cancers

People with CLL can develop any type of cancer, and in addition to a higher risk of skin cancers they have an increased risk of:

- Cancer of the larynx
- Lung cancer

- Colon cancer
- Kaposi sarcoma
- Soft tissue sarcoma

d. Risk of other disorders

CLL treatment is thought to increase the chance of other bone marrow and blood disorders.

III. Auto-immune haemolytic anaemia

This is a condition in which your immune system does not recognise your red blood cells as your own and destroys them, causing you to become anaemic. *Auto-immune* 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 auto-immune 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 auto-immune problems, usually starting with steroid therapy.

6 Living with CLL

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

I. Emotional impact and management of a CLL diagnosis

Being told you have cancer can be very upsetting. CLL is an uncommon condition. Being diagnosed with CLL can affect you as a whole, not just your body. 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, 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.

It is also important that you feel able and empowered to discuss these responses with your GP and your haematologist. This is an important part of expansive, patient-centric healthcare in the context of CLL and other cancers. Don't ever feel you are 'bothering' your doctor or nurse with your concerns or questions: you have every right to their help, and the more informed you are about your CLL, the more readily you'll be able to get on with your life.

CLL does not always need treatment, particularly initially. When treatment is needed, it may be extended over months (*FCR* is six months), or continuously (*ibrutinib* is taken every day).

'Watching and waiting'

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's 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, and you feel hopeless, and lose interest and pleasure with things in life, then you may have significant depression. Your first steps should be to speak to your loved ones about your mood and state of mind, and contact your GP or specialist.

You may lift the way you feel by engaging in activities that you were enjoying before the diagnosis and connecting back with your usual 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.

II. 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 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, using laptops, tablets or mobile phones, or watching TV dramas.
- 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. Yoga or pilates may also help with this.

III. Talking about CLL

a. Talking to your haematologist and healthcare team

CLL, although the most common form of leukaemia in adults, is still an uncommon condition. It is important for you to develop a good working relationship with your haematologist and healthcare team.

Here are some suggestions to consider:

- 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 dealing with my feelings?

– Bring someone along to your appointment. They can provide support, ask questions and take notes.

– It can also be useful to repeat back what you have heard, to be sure you have fully understood it, or write it down during the appointment.

– Be open when you discuss your symptoms and how you are coping. Good patient-doctor communication tends to improve outcomes for patients.

b. Alternative and complementary therapies

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, and or

– you choose to start any form of complementary therapy outside of your medical treatment. You should 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.

c. Talking to family and friends about your CLL

You may want to let your close family and friends, and perhaps your employer know about your health condition, but CLL can be hard to explain. The easiest way may be to provide them with basic information and give them information leaflets or booklets about CLL like this one, if they want more in-depth information. The CLLANZ website has a lot of useful information (https://clladvocates.nz/).

It is probably best to focus conversations on the symptoms you're experiencing, how the condition affects you and how you feel about it. Often people misunderstand and it will probably 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 may not be what you really want to hear. In many ways, the more you communicate with them the better.

It may help you to 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
- your symptoms (maybe you are tired)
- what you need (maybe more help day-to-day, or someone to talk to)

- 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 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:

i. 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.

There are many useful cancer organisations and blood cancer charities in New Zealand, the UK, Australia, Ireland, and the USA. See a list of these on page 42.

ii. 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.

iii. 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. 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.

iv. 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.

IV. 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.

V. Financial help

You can discuss with your health care providers which benefits you are eligible for. You may like to talk to a benefits advisor. There are also possibilities for provision of financial assistance. Find out about this at https://www.govt.nz/browse/health/financial-help/financial-help-for-people-with-disabilities/

VI. Survivorship

Survivorship is a term to describe someone who is living with a cancer diagnosis and may be in remission or cured.

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 help you manage. Survivorship also focuses on your health and life with cancer after the end of treatment, either in remission, or continuing disease and palliation until the end of life.

VII. 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. Palliative care services will be provided by your local hospital and district nurses, and you may receive day-to-day care at your home and at the hospital.

VIII. 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.

7 Useful contacts and further support

There are many useful cancer organisations and blood cancer charities including ourselves in New Zealand, the UK, Australia, Ireland and the USA. These include:

- **CLL Advocates New Zealand** Visit us at www.clladvocates.nz or contact neil@clladvocates.nz and join our private Facebook group at https://www.facebook.com/groups/cllanz
- **Leukaemia & Blood Cancer New Zealand (LBC)** – a national organisation providing patient support for all blood cancers www.leukaemia.org.nz
- **CLL Support (UK)** – a national patient-led UK charity www.cllsupport.org.uk
- **Patient Power** – a USA-based patient information and support group covering all cancers www.patientpower.info
- **Leukaemia Care (UK)** – a UK-based charity covering all leukaemias www.leukaemiacare.org.uk
- **CLL Advocates Network** – an international collective of CLL patient advocacy groups from New Zealand, Canada, Czech Republic, France, Israel, Portugal, UK and the United States https://www.clladvocates.net/
- **Cancer Society New Zealand** – www.cancernz.org.nz

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