Relapse in Chronic Lymphocytic Leukaemia (CLL)

A Guide for Patients

Leukaemia Care
YOUR Blood Cancer Charity

Introduction

A relapse is the return of leukaemia after treatment. Specifically, this booklet is about a relapse in chronic lymphocytic leukaemia (CLL).

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

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In this booklet

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 supported by our Patient Advocacy team from 8.30am - 5.30pm on weekdays. A nurse is available on Mondays from 9.00am - 5.00pm, Tuesdays to Thursdays 9.30am - 2.00pm and Thursday and Fridays evening from 7.00pm - 10.00pm. If you need someone to talk to, call **08088 010 444**

Nurse service

We have two trained nurses on hand to answer your questions and offer advice and support, whether it be through emailing **nurse@leukaemiacare.org.uk**, 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.leukaemiacare.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.leukaemiacare.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@leukaemiacare.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.leukaemiacare.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@leukaemiacare.org.uk**

Patient magazine

Our quarterly magazine includes inspirational patient and carer stories as well as informative articles by medical professionals. To subscribe go to **www.leukaemiacare.org.uk/communication-preferences/**

What is Chronic Lymphocytic Leukaemia?

In chronic lymphocytic leukaemia (CLL), the lymphocytes in the bone marrow start multiplying excessively leading to large numbers of abnormal, immature cells called blasts, which prevent the bone marrow from producing enough healthy blood cells of all types. Lymphocytes are a type of white blood cell involved in the immune response.

There are three types of lymphocytes:

1. B-cells produce antibodies that seek out and immobilise bacteria, viruses, and toxins which invade the body.
2. 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 (NK)-cells attack cancer cells and viruses.

All these types of white blood cell are found in the blood, bone marrow, and lymphatic system. The lymphatic system is a part of the immune and circulatory systems. A network of small lymphatic vessels, which run adjacent to the small blood vessels in the body, drain lymph fluid from all over the body to clear excess fluid and act as a blood filter helping to fight infection with the help of the B-cells and T-cells.

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

Full details of the characteristics, diagnosis and treatment of CLL are given in the Patient Information Booklet titled chronic lymphocytic leukaemia (CLL), which is available on the Leukaemia Care website at

https://www.leukaemiacare.org.uk/support-and-information/help-and-resources/information-booklets/

In this booklet, relapse in CLL will be examined.

What is relapsed CLL?

In patients with CLL who require treatment, the mainstay of the treatment is chemo immunotherapy, which consists of chemotherapy to which immunotherapy is added. Where the CLL cells have a particular chromosome abnormality, such as a 17p deletion or TP53 mutation, a novel agent such as ibrutinib is used instead of chemotherapy.

The nature of CLL as a chronic disease means that it is not a curable disease, and that a relapse is expected to happen at some point. A relapse is when a patient initially responds to leukaemia therapy but, after six months or more, response to treatment stops. This is also sometimes called a recurrence. Refractory CLL occurs when the cancer has not responded to first-line treatment (first treatment given).

Remission can be established by examining:

- **Blood samples (haematological remission):** Blood counts return within normal ranges.
- **Blood and bone marrow at the cell level (cytogenetic remission):** Diseased cells have been greatly reduced, or no longer appear, in the bone marrow.
- **Blood and marrow at the molecule level using sensitive tests such as polymerase chain reaction analysis or flow cytometry (molecular remission):** No evidence of disease in the blood cells and/or bone marrow is seen at all.

Why does relapse happen?

While the recent treatment of CLL with chemo-immunotherapy has resulted in improved patient responses and overall survival compared to chemotherapy alone, a sizeable number of patients will still relapse and need subsequent treatment.

Relapse is often linked to the cause of the CLL, particularly when chromosome mutations are involved. These genetic characteristics are useful for predicting how the CLL will progress, and which patients will

respond to therapy or relapse.

For patients with CLL, analysis of chromosomes has detected several reoccurring mutations:

- 13q deletion - 55% of patients
- 11q deletion - 18% of patients
- 17p deletion - 7% of patients previously untreated and 30% of patients who relapsed
- Trisomy 12 (3 copies of chromosome 12) - 16% of patients

Patients with 13q deletion tend to have good prognoses and patients with trisomy 12 have an intermediate prognosis. Therefore, these patients may be more fortunate in avoiding relapses.

Patients with 11q deletion and 17p deletion are known to have a shorter time before relapse where further treatment will be required.

Deletion of chromosomal region 17p13 results in the loss of one of the variants of the TP53 gene. This abnormality is predictive of a poor response to treatment and is associated with the shortest time before relapse compared with standard CLL patients and patients with lower-risk chromosomal abnormalities.

Another indication of a reduced survival rate in CLL is an unmutated immunoglobulin variable region heavy chain (IgVH) gene. This gene is responsible for generating antibodies used by the immune response. IgVH mutation status has identified two subtypes of CLL that have a differing clinical course:

1. Patients with a mutated IgVH have a subtype of CLL which is slow to progress and with little symptoms. These patients have a better prognosis.
2. Patients without a mutated IgVH have an aggressive subtype of CLL with a poorer prognosis, a shorter duration of complete remission and a greater chance of relapse.

The mutation status of IgVH can be detected by DNA sequencing. DNA sequencing involves determining the exact order of the four organic molecules (also called nucleotides: adenine, guanine, cytosine, and thymine)

What is relapsed CLL? (cont.)

which make up a molecule of DNA.

How often does relapse occur?

Despite the encouraging responses in patients with CLL who have received chemo-immunotherapy, most patients will relapse at some point within the first five years of starting treatment.

The first-line chemo-immunotherapy regimen of FCR (combination of fludarabine, cyclophosphamide and rituximab) is most frequently used in patients with CLL, as long as they are fit and well with little or no other health problems. However, even after this treatment regimen, approximately 6% of patients will relapse within six to 12 months and another 14% will do so within two years.

Patients whose first remission lasts less than three years have a short survival period, whatever treatment they were given subsequently. For patients with a first remission greater than three years, a number of other treatments are available. The average remission after FCR as a first line treatment is around five years. When it has been identified that the disease has come back, further treatment options will be discussed with you by your doctor. Details of these are given in the section **'How is relapsed CLL treated?'**

Symptoms and diagnosis of relapsed CLL

What are the symptoms of relapsed CLL?

The course of CLL can be very varied. CLL usually develops extremely slowly, and more than half of all patients do not have any symptoms in the early stages of the disease. 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).

In patients with CLL who relapse, the symptoms and signs that may occur are similar to those for newly diagnosed CLL, and include:

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

How is relapsed CLL diagnosed?

The majority of relapses in patients with CLL are diagnosed relatively early on because after first-line or second-line treatment, patients are monitored regularly. The diagnosis of relapsed CLL is similar to that of the initial diagnosis.

Diagnosis of CLL requires the presence of increased levels (≥5000 per mm^3) of monoclonal (genetically identical) B-cells in the blood for at least three months. The clonal nature of the circulating B-cells should be confirmed by flow cytometry (a test that identifies specific

surface markers on the cell).

Diagnosis is achieved using the following tests:

Complete blood count

Detects the number of red blood cells, white blood cells and platelets.

Peripheral blood smear

Blood sample is viewed under a microscope to count different circulating blood cells, and see whether the cells look normal.

Bone marrow aspiration and biopsy

The aspiration procedure removes a liquid marrow sample and the biopsy removes a small amount of bone filled with marrow. Medication is given to numb the area, or a general anaesthetic is performed, in order to remove a sample from the hip bone. These samples can be examined for:

- Percentage of lymphoblasts in the bone marrow
- Any abnormalities of the lymphocytes
- Immunophenotyping: This procedure identifies the types of proteins on the surface of the lymphoblast cells

Immunophenotyping

Immunophenotyping is used primarily to help diagnose and classify leukaemias and lymphomas, and guide their treatment. Where possible, it may be able to predict the aggressiveness of the leukaemia and its responsiveness to certain treatment.

Markers detected on the cells will help characterise any abnormal cells present. In conjunction with the patient's clinical history, physical examination, signs and symptoms, and laboratory tests, immunophenotyping can help make a diagnosis.

Immunophenotyping is routinely performed by flow cytometry which processes either blood, bone marrow fluid or tissue by adding specific antibodies that have been tagged with fluorescent markers. These antibodies, also called cell markers, bind to corresponding antigens on the lymphocytes. The flow cytometer rapidly measures the size and internal cellular structures

Symptoms and diagnosis of relapsed CLL (cont.)

of thousands of cells, and assesses the type and quantity of fluorescent antigen-antibody complexes present. For these practical reasons, flow cytometry is preferred to immunochemistry for immunophenotyping.

Chromosomal or cytogenetic analysis

- Blood smear samples can be used to identify certain changes in the number and size of chromosomes within cells that might have led to the relapse.
- This can be achieved easily and accurately with fluorescent in situ hybridisation (FISH) which uses fluorescent dyes to attach to certain parts of chromosomes. FISH analysis should always be carried out prior to a patient receiving treatment as it can determine types of leukaemia likely to relapse or their response to treatment.

The following tests and procedures are carried out to confirm the diagnosis, confirm the stage of the CLL, and enable your consultant to determine the treatment you are most likely to benefit from:

- **Lumbar puncture** - This is used to determine if the lymphoblast cells are in your central nervous system (brain and spinal cord).
- **Imaging tests** – Ultrasound and computed tomography scanning to accurately detect the enlarged lymph nodes, liver and spleen before starting treatment.
- **Lymph node biopsy** – This is carried out when 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 examined under a microscope. This is usually performed as a day case and does not require a hospital stay.
- **Staging** - This is a grading system used by consultants to describe the extent of the CLL, in terms of location, its effect on the blood count, and the number and size of existing lymph nodes. Grading CLL helps your doctor predict how quickly the cancer may grow and spread, as well as decide the best treatment for you. There are

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

How is relapsed CLL treated?

To date, the FCR treatment regimen has given the best complete remission rate, longest duration of remission, and the most extensive survival for patients with CLL. The regular chemo-immunotherapy regimens for the treatment of patients with CLL are FCR or the combination of bendamustine and rituximab. However, with both these regimens, patients may experience significant side effects, especially older patients or those with other health issues.

Most patients who respond to treatment will eventually relapse and require second-line therapy (treatment other than the type used the first time around). However, patients who are in remission for less than three years the first time have shorter periods of remission and shorter intervals between treatments, whatever treatment regimen they were given subsequently.

The most appropriate treatment for relapsed patients depends largely on the characteristics of their CLL, and is also dependent on their prior therapies, best response obtained with previous treatment, length of the response, and their characteristics at the time of relapse.

Alternative treatment options

Most patients with relapsed or refractory CLL require second-line therapy (treatment other than the type used the first time around). Second-line drug regimens may include:

- Chlorambucil with a monoclonal antibody (if the patient only received chlorambucil on its own as first line therapy)
- Targeted therapy: ibrutinib or idelalisib in combination with rituximab (when the disease has been treated but relapsed within 24 months)
- Venetoclax
- Clinical trials may also be a possibility if suitable and available

Chlorambucil with a monoclonal antibody (chlorambucil chemo-immunotherapy)

If patients only received chlorambucil as first-line therapy, then chlorambucil with a monoclonal antibody can be an alternative treatment for patients who relapsed. Chlorambucil is a type of chemotherapy called an alkylating agent which interferes with DNA and stops cancer cells proliferating.

When combined with other monoclonal antibody drugs such as ofatumumab or obinutuzumab, chlorambucil was superior to chlorambucil alone in two large phase 3 studies.

Targeted therapy

Patients with 17p deletions or TP53 mutations, for whom chemo-immunotherapies are not suitable, can be treated with the targeted therapies B-cell receptors inhibitors such as ibrutinib and idelalisib, or B-cell lymphoma-2 inhibitors such as venetoclax.

Ibrutinib is an inhibitor of Bruton's tyrosine kinase, and idelalisib is a selective inhibitor of the delta phosphatidylinositol 3-kinase enzyme. Both these targeted therapies inhibit specific signalling pathways for B-cells.

Idelalisib has regulatory approval, when used in combination with rituximab, in previously-treated CLL and CLL with 17p deletion or TP53 mutation that cannot be treated with any other therapy. It is approved by the National Institute for Health and Clinical Excellence (NICE).

Ibrutinib has regulatory approval for previously-treated CLL and untreated CLL with 17p deletion or TP53 mutation, and is also approved by NICE.

Both ibrutinib and idelalisib are effective in patients with high-risk features and are able to control CLL in difficult-to-treat patients better than currently approved therapies. This makes them the drugs of choice for CLL patients with TP53 mutations and patients resistant to chemo-immunotherapy. Both idelalisib

How is relapsed CLL treated? (cont.)

and ibrutinib in combination with monoclonal antibodies have improved survival in relapsed/refractory CLL.

Idelalisib in combination with rituximab

Idelalisib is currently only approved for relapsed/refractory CLL when combined with rituximab, based on the pivotal phase 3 trial which compared treatment with the combination against rituximab alone. In this randomised trial, the investigators recruited 222 patients >65 years, who had been treated with first-line treatment but relapsed within 24 months, and had decreased renal function as well as previous therapy-induced myelosuppression. Treatment with the combination of idelalisib and rituximab, when compared with rituximab alone, significantly improved overall response and overall survival at 12 months in patients with relapsed CLL who were less able to undergo chemotherapy. The clinical benefit of this drug was also present in the high-risk patients with del (17p) and/or TP53 mutation.

Ibrutinib

The approval of ibrutinib as initial therapy for CLL patients was based on the phase 3 RESONATE 2 trial in which 269 previously untreated CLL patients >65 years received ibrutinib or chlorambucil. After a follow-up period of 18.4 months, patients on ibrutinib showed a significant increase in overall survival with an estimated survival rate at 24 months. Overall response rate was also significantly improved with ibrutinib compared with chlorambucil. Complete remission was achieved by five patients receiving ibrutinib compared with two patients receiving chlorambucil.

Positive responses with idelalisib and ibrutinib are increasingly being reported in patients with relapsed/resistant CLL. However, for a number of patients with relapsed CLL, who were classified as high-risk, these therapies do not achieve a long-term response.

Venetoclax

Venetoclax is an inhibitor of the activity of a protein called

B-cell lymphoma-2. This protein regulates the natural death of cells, particularly cancer cells. In the United Kingdom, venetoclax has conditional approval for CLL when other treatments have failed or are unsuitable. Conditional approval for marketing authorisation (available for prescription) was granted because additional data is being considered; however, the use of venetoclax in the interest of public health and the benefit of immediate availability outweighs the risk from less comprehensive data than normally required.

NICE recommends the use of venetoclax in patients with a 17p deletion or TP53 mutation, and whose disease has progressed despite treatment with chemo-immunotherapy and a B-cell receptor inhibitor.

In a phase 1 study to determine the best dose of venetoclax to use in safety and efficacy trials (dose-escalation study), the overall response rate across all doses of 116 patients who received venetoclax was 79% with a complete response achieved in 20%.

Rechallenge with first-line treatments

Patients with CLL who have relapsed can be re-challenged with the first-line treatments of FCR or the combination of bendamustine and rituximab, but this is extremely rare.

FCR

For patients without the high-risk features for being refractory to therapy or having chromosome 17 abnormalities, FCR is an effective and safe therapy. For high-risk and elderly patients, optimal treatments still need to be defined.

Bendamustine and rituximab combination

For the many CLL patients >65 years who experience severe toxicity with FCR (because of the serious infections and suppression of the bone marrow), bendamustine combined with rituximab (BR) is commonly used as it is better tolerated.

How is relapsed CLL treated? (cont.)

Allogeneic stem cell transplantation

The treatment options described previously may render allogeneic stem cell transplantation (ASCT) outmoded because patients can now be maintained in a prolonged disease-free state with these treatments, even if they are not curative. However, especially for young healthy patients, ASCT remains the only potentially curative option if they are fortunate enough to have a suitable donor. ASCT is rarely offered to patients aged >70 years. Clinical practice recommendations for the role of ASCT in the current management of relapsed CLL has relegated its use to later in the disease. A recent paper summarising the clinical findings of physicians with expertise of ASCT in CLL has recommended ASCT for patients with the following:

- CLL which is refractory or progresses despite treatment with B-cell receptor inhibitors
- CLL in high-risk patients which does not respond to two lines of treatment and shows an objective response to B-cell receptor inhibitors or to treatment in a clinical trial
- CLL which does not show an objective response or progresses after B-cell receptor inhibitors, regardless of whether an objective response is achieved

Supportive therapy

Supportive therapy or palliative care is valuable during treatment in each phase of CLL to offset any complications, particularly for patients with high-risk features. Supportive therapies given during treatment for relapsed CLL may include antibiotics, antivirals, or antifungals to combat infection, and leukapheresis to separate out large numbers of white blood cells from the blood. For more details, see the **palliative care** section later in the booklet.

Clinical trials

For some patients, including those with poor treatment responses associated with the

del17p mutation, TP53 mutation and a lack of mutated IgVH, participation in clinical trials can offer another treatment option, as clinical trials are currently making excellent progress in the treatment of CLL. Moreover, clinical trials represent a strong contribution to CLL management, as well as access to newer medications which may not be available on the NHS, and the possibility in the future with the development of new treatments.

Details of trials in the treatment and management of CLL which are recruiting patients can be found online at **clinicaltrials.gov**

Prognosis

The majority of patients will experience a relapse within five years of starting chemo immunotherapy, and for patients with a duration of first remission less than three years prognosis is worse. However, on the whole, CLL is not seen to have an impact on natural lifespan.

Your prognosis will vary according to the phase of your CLL, your response to treatment and your state of health. It is possible that your CLL will progress slowly and remain controlled with targeted therapy. Alternatively, you may go into remission for many years, during which time you will not have any symptoms and your blood tests will be clear.

In the event of a relapse, you will be offered further treatment to help you reach a second remission. If the new targeted therapies are not successful, you may be offered intensive treatment with an ASCT, depending on your age and state of health, but this is rare due to the further treatments options that are now available.

The two most important genetic prognostic markers for CLL that significantly affect the course of the CLL and the likelihood of relapse are:

- Chromosome 17 deletion 17p, del(17p), which occurs in 30% of patients who relapse
- TP53 mutations and/or no IgVH mutation

How is relapsed CLL treated? (cont.)

The poor treatment responses, and shorter time before relapse associated with the del17p mutation, TP53 mutation and lack of mutated IgVH are the focus for using new therapies to treat CLL.

Seeing your doctor

Your symptoms

Whatever symptoms you have, make sure you write a list of all of them to share with your doctor as they may be important to your treatment.

Your appointment

Arranging an appointment with your general practitioner (GP) or your consultant will be one of the first things you will need to do when you start to notice symptoms. Pick a time convenient for you that you know you will be able to attend. If there is a chance that you might be experiencing a relapse, you will be referred to the hospital who will be able to confirm this through tests.

Your preparation

It is important to know exactly what you would like to ask your doctor. Make a list of your questions and leave spaces for the answers so you can write them down when you see the doctor. This way you can go into the meeting ready and prepared.

Examples of questions to ask the doctor:

- How would I know if I my CLL came back?
- What tests will I need to have?
- What will the tests show?
- How long will it take to get the results back?
- How common is it to have a relapse?
- What sort of treatment will I need?
- How long will my treatment last?
- How will I know if my treatment has worked this time?
- What will the side effects be?
- Are there any foods or medications I need to avoid?
- 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?

Talking to your doctor

Be honest with your doctor; they have seen and heard everything before, so there is no need to feel embarrassed about anything. If you saw your healthcare team before seeing your doctor, be sure to share with your doctor everything your healthcare team told you about your relapse, the blood tests you had performed, and the next steps in your CLL journey.

If you want to, ask if you will receive more intensive treatment or palliative care. However, it is important to remember that this is only offered if other lines of treatment are exhausted or you decide you no longer want further treatment. It is increasingly rare for patients to die due to their CLL.

Your support

If it helps, take a family member or friend in with you for support. Some people take a pen and paper in to make notes, and repeat back to their doctor everything they have been told to ensure that they are both on the same page and that nothing has been missed or forgotten.

The next steps

Always ensure that you leave the GP surgery, or the hospital, having shared everything you know about your condition, with all of your questions answered, and knowing exactly what the next steps are, whether it is more tests, further treatment or palliative care. You can ask for a summary letter of the consultation to have everything in writing. Your doctor will generally send a letter like this to your GP.

Furthermore, be sure to access all of the other support available to you as this may be able to help you with your feelings towards your diagnosis and treatment.

Telling your family

Planning who to tell

Telling your family and friends that you have suffered a relapse can be difficult, especially since you already went through it with your initial CLL diagnosis. One positive aspect to this is that you already have your team in place, so once they know what your situation is, they can help and support you like they did before.

You may want to create a list of people you want to tell, starting with close family and friends, and then extending it beyond, from your colleagues at work to friends in your neighbourhood.

Planning what to say

It is important to know what you want to say and exactly how much you want people to know. Being clear in your mind about that before speaking to anyone will make this a much smoother experience. Know your story that you want to tell, the diagnosis, the prognosis, the next treatment steps, and what you expect to be going through physically and emotionally. Be sure to speak to people in an environment where both of you can hear each other clearly and where there are likely to be no interruptions.

How to say it

Although it is upsetting that you have relapsed and the people you tell may get upset for you, it is important to try and remain positive and optimistic when talking. Even though a relapse is unfortunate, it is not the end of the world, as there are further treatment and supportive care options available.

How to respond

You may receive similar responses to when you told people about your initial diagnosis. Naturally they will feel sad, and concerned for you. Everyone deals with this type of news in their own way, from shock and silence, to questions and support.

Invariably, people respond positively, which in turn means you will respond back positively.

Accepting help

Sometimes people feel guilty for their cancer relapsing, that they weren't strong enough, 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 in the next stages of your CLL journey. 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.

Repeating yourself to different people can become burdensome, which is where 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 speak to your friends and family following a relapse. You can visit **www.leukaemiacare.org.uk**, or call **08088 010 444**, to find out more.

Managing your emotions

Being told that your cancer has returned may be difficult for you to deal with, especially after all your time and effort during treatment and remission period.

Indeed, you may have a positive demeanour, which will obviously be helpful to you during the next steps in the management of your CLL. However, you may experience a range of emotions, including uncertainty, isolation, anxiety, anger, sadness and depression. Understanding each emotion and developing ways that help you deal with them will help you move forward with your life.

Uncertainty

You may think "What happens next?". You may be unsure about your health and what the future holds for you. You may or may not have had meetings with your healthcare team to discuss the next steps following your relapse. 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 following relapse and carrying on with your life will help ease any anxieties. Help, care, kindness and support will be available to you from your healthcare team, and you will have access to counsellors and therapists when you need it.

Isolation

If you have received a diagnosis of relapse, and the next steps don't involve intensive treatment, you may feel a break in your routine. You may feel alone because you will no longer enjoy regular meetings with your healthcare team who provide you with information and reassurance, or fellow patients who can provide you with empathy and compassion.

Alternatively, you may feel this break in routine allows you to be around those closest to you, and follow your regular routine of work and play. Being around those closest to you, such as your family and friends, can be positive and negative.

Let them 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.

Anxiety

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. These things help us to face a danger or run away. These changes in you are part of the 'fight or flight' response. Any feeling of discomfort, pain or even another appointment with your healthcare team may elicit such responses, and give you sleepless nights or feelings of worry. This is completely natural.

Such reflexes and 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. Cognitive behavioural therapy can help you deal with your worrying thoughts.

Anger

Feeling angry after a relapse is natural and normal. You may be angry with yourself, your body, with the healthcare team or with family and friends. You may display your anger as impatience, irritability and frustration with people and things that would not normally bother you.

Understanding exactly what is making you angry will help you deal with your feelings effectively. In addition, setting yourself achievable goals that stretch you will help reduce the anger and impatience you feel, 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 your energy positively with no negative impact on your body. Talking

Managing your emotions (cont.)

about your feelings, letting them out, will also help stop you lashing out at people and keep you calm.

Sadness and depression

Relapsing will bring back some, if not all, of the feelings you felt when you were first diagnosed with your CLL. You may feel a sense of loss of the person you used to be, and how safe you felt. You may also feel that your illness is a heavy burden on those around you. You might be feeling low, which is a natural effect of your illness, treatment and recovery. 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 around you 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 your relapse and initial diagnosis, to connect 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. If you have made any acquaintances or friends in the same position as you, talk to them over coffee as they will understand exactly what you are facing.

Self-confidence

Being forced to readjust from your daily routine during remission back into one involving multiple visits to the hospital for further treatment, or moving into palliative care, can take its toll. This interruption of your life, along with your lack of energy because of your CLL and the effects of your treatment, can impact on how you feel about your appearance and how you feel emotionally. In turn, this can knock your self-confidence and self-esteem. Your feelings of relief, hope, and optimism have just been replaced with their polar opposites.

You can gradually build your self-confidence and self-esteem back up by engaging in the activities

you did before your diagnosis, and socialising with family, friends, and fellow patients. This will help create a supportive atmosphere to get you back to your old self.

Mindfulness and relaxation

Simple practices from mindfulness and relaxation techniques can help you calm the mind, release tension and ease any pain in your muscles.

- 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.

By taking some time out of your day to do these exercises, you can help quieten your mind and remove the stress of coming to terms with your diagnosis, so you feel calmer and more relaxed.

Survivorship

Someone who is living with or is beyond a cancer diagnosis can be considered a cancer survivor.

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, especially if you are relapsing after remission, you will face new challenges to cope with from physical to psychological and social ones. Survivorship aims to provide personalised care based on your need to improve 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 until the end of life. At this point, your routine of meeting frequently with your healthcare professionals also ends, so you may feel a mixture of emotions from relief to fear, anxiety and uncertainty about the future. You may wonder how you will slot back into your life after coming through the treatment period.

Your survivorship pathway began at the point when you were diagnosed with CLL. By this point, you will have been starting to receive support for work, finance, and personal relationships through to managing pain, fatigue and making positive lifestyle changes, such as starting a healthy diet and gentle exercising.

Your individual needs as a patient will be identified and addressed, including:

- Dealing with the emotional impact of receiving a diagnosis of relapse which may have created feelings of uncertainty, fears of recurrence and difficulties in planning for the future. These will be discussed with you to develop your

individualised care plan with support from social care staff and therapists, as you need it.

- Improving your quality of life through efficient and co-ordinated care during your treatment, with effective communication within the treatment team, and a positive attitude.
- Taking care of any comorbidities – that is, other medical conditions and diseases – and offering you cancer rehabilitation based on your clinical needs as assessed by informed professionals, and ensuring compliance with the National Cancer Rehabilitation Pathways.
- Providing you with a treatment summary from diagnosis of your relapse to the end of your treatment. This would include any ongoing medication and noting possible symptoms that may occur in the future. You would also be provided details of who to contact in addition to your GP for any concerns you may have.
- Preparing you fully for the impact of relapse and treatment, the physical and physiological side effects of treatments and the psychological impact of CLL relapse in general. You will be provided physical equipment, and taught about various coping strategies to adapt to your new situation.
- Supporting you with advice for social and financial difficulties, including caring responsibilities, your inability to participate in social activities, any debt and financial worries from not being able to work, and perhaps the need to return to work before you feel ready.
- Receiving health and nutrition advice from a nutritionist on following a healthy and balanced diet to help improve your general health and wellbeing. The World Cancer Research Fund published a report for cancer survivors which suggests that even small dietary and lifestyle changes can produce large health benefits.

Palliative care

Palliative care in relapsed CLL

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

Palliative care aims to reduce your symptoms, control your CLL, extend your 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.

Who provides palliative care?

Your palliative care will be provided by a team of health and social care professionals trained in palliative medicine who will coordinate your 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. Your 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.

What is the clinical course?

You will have experienced a protracted cycle of relapses and remissions, and be prone to frequent infections because of the CLL and the impact of your treatments. Your chemotherapy may continue because of potential remission and/or useful palliation.

You may experience various pains and other clinical complications such as:

- **Bone pain**: Radiotherapy and/or oral steroids, and sometimes non-steroidal anti inflammatory drugs (NSAIDs), may be used, although these are used with caution because they can interfere with your immune system and kidney function.
- **Bone marrow failure**: Blood

and platelet transfusions are provided to prevent and fight recurrent infections and bleeding episodes.

- **Oral problems**: Analgesic mouth washes and topical ointments may help with ulceration. Chewing gum, and mouth washes have been shown to help with dry mouth, dental caries and oral thrush.
- **Night sweats and fever**: These can place a heavy burden on carers because of so many changes of night clothes and bedding.
- **Pathological fractures**: Orthopaedic intervention and subsequent radiotherapy, with consideration given to prophylactic pinning of long bones and/or radiotherapy to prevent fractures will be performed. This will reduce the likelihood of complex pain syndromes developing.
- **Spinal cord compression**: Immediate high single daily dose oral steroids will be given.
- **Back pain from wedge and crush fractures of the vertebrae of the spinal column**: Treatments can include analgesics, antidepressants and/or anticonvulsant medication used in tandem with opioids.
- **Hypercalcaemia**: Treatment is usually with intravenous hydration and intravenous bisphosphonates.
- **Loss of appetite**: Low-dose steroids may temporarily boost the appetite, while small, frequent and appetising meals and supplement drinks will also help.

End of life care

When does end of life care begin?

If you have relapsed and are going through palliative care, you may be offered end of life care. End of life care begins when you need it and may last a few days, months or years.

What does end of life care involve?

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 you enjoy a good quality of life until you die, and to die with dignity. The professionals looking after you will ask you 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 you are, you will receive high quality end of life care.

Who provides end of life care?

A team of health and social care professionals may be involved in your end of life care, including hospital doctors and nurses, your GP, community nurses, hospice staff and counsellors, social care staff, physiotherapists, occupational therapists or complementary therapists, and religious leaders, if you would like this. If you are being cared for at home or in a care home, your GP will have overall responsibility for your care with the support from community nurses, along with your family and friends.

What choices do I have in terms of end of life care?

Deciding where you want to die can be a difficult choice to make. Working out what you and your loved ones want, together with seeing what services are available to you can help to make the decision a little easier.

- **Staying at home** - A place of familiarity, surrounded by your loved ones, may be something

that you will find reassuring. External care professionals will be able to visit you at home to make sure your symptoms are looked after.

- **Hospices** – Specialised in looking after those with life-limiting illnesses and those who are coming to the end of their life, hospices are staffed with care professionals who are able to keep an eye on you, make sure that your symptoms are controlled and offer you a number of services to make your stay as comfortable as possible. For more information on the care that they can provide, go to **https://www.hospiceuk.org/**
- **Residential care/nursing homes** - If you think that your stay may be a few months or more, then a nursing home may be more suitable than a hospice. These can be private or run by a charity or the local council so be sure to check if there are any fees.
- **Hospitals** - Although you may be used to staying in a hospital ward, the care routine cannot always be tailored to your specific needs. Pressures on the NHS mean that your stay will only be as long as strictly required. As soon as the condition you were admitted for has been resolved, you will need to go back to your home or nursing home. However, a number of specialists will be available to help look after you for specific problems, and a number of hospitals also have a designated palliative care team for patients who require them.

Whatever your choice, speak with your GP or healthcare team who will able to help you put everything into place.

Glossary

Allogeneic Stem Cell Transplant (ASCT)

Stem cell transplant of cells from a matching donor.

Amino Acids

Organic molecules which are the building blocks for making proteins.

Anaemia

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

Antibody

Protein produced by the B-cell lymphocytes in response to a specific antigen, such as a bacteria, virus, or foreign substance in the blood.

Antigen

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

Blasts

Patients with leukaemia have a high number of abnormal white blood cells. These white blood cells are not fully developed and are called blasts or leukaemia cells.

Bone Marrow Failure

Term used when the bone marrow is unable keep up with the body's need for white and red blood cells and platelets.

Central Nervous System

Part of the nervous system which includes the brain and spinal cord.

Chemotherapy

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

Chromosomes

Thread-like structures which carry the genes, and are located in the nuclei of every cell in the body. There are 46 chromosomes (23 pairs) in humans.

ClinicalTrials.gov

ClinicalTrials.gov is a database of trials and includes details of 276,190 research studies in 204 countries.

Clonal

Refers to an organism descended from, and genetically identical, to a single common ancestor.

Complete remission

Complete remission is said to have occurred when the following conditions have been met:

- Blood cell counts returned to normal
- Less than 5% of blasts (abnormal, immature, early lymphocytes) are still present in the bone marrow
- There is no leukaemia present elsewhere in the body

Cytogenetics

Branch of genetics that is concerned with how the chromosomes relate to cell behaviour, particularly to their behaviour during division and reproduction.

Cytotoxic Drugs

Drugs that are toxic to cancer cells and prevent their growth and replication.

DNA (Deoxyribonucleic Acid)

Thread-like chain of amino acids found in the nucleus of each cell in the body which carries genetic instructions used in the growth, development and functioning of the individual's cells.

Fatigue

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

Flow Cytometry

Technology used to analyse the physical and chemical characteristics of particles in a fluid as it passes through at least one laser. Cell components are fluorescently labelled and then excited by the laser to emit light at varying wavelengths.

Fluorescence in Situ Hybridisation (FISH)

Process using fluorescent dyes to attach to certain parts of chromosomes for their identification.

Genes

Genes are made up of DNA which stores the genetic information required to make human proteins.

Immunophenotyping

Process that uses antibodies to

Glossary (cont.)

identify cells based on the types of antigens or markers on the surface of the cells. This process is used to diagnose specific types of leukaemia and lymphoma by comparing the cancer cells to normal cells of the immune system.

Immunotherapy

Treatment that uses the body's own immune system to fight the cancer.

Leukopenia

Abnormally low number of white blood cells in the blood.

Leukaemia

A group of cancers that usually begin in the bone marrow and result in high numbers of abnormal white blood cells. These white blood cells are not fully developed and are called blasts or leukaemia cells. Depending on the type of white blood cell involved, there are different types of leukaemia with varying characteristics, such as being acute (develop quickly) or chronic (develop slowly).

Lymph Nodes

Components of the lymphatic system (part of the body's immune system) that contain lymphocytes which produce antibodies and macrophages to digest dead cells. Lymph nodes are swollen with cell fragments in the event of infection or cancer. They are located mainly in the spleen but also in the neck, armpit and groin.

Minimal Residual Disease (MRD)

Measure of the presence of leukaemia at a molecular level rather than at a cell level. It is measured using molecular techniques such as flow cytometry and polymerase chain reaction analysis.

Morbidity

Refers to having a disease or a symptom of a disease.

Phase 1 Trial

Small trial (up to 30 volunteers) to confirm if the drug behaves as expected, determine its side effects, and how the body reacts to the drug.

Phase 2 Trial

Medium trial (up to 100 volunteers/patients) to confirm

the drug's safety, find the best dose to use, assess the drug's effectiveness if the trial is in patients, and determine the value of studying it in large numbers of patients in a Phase 3 trial.

Phase 3 Trial

Large clinical trial (more than 100 patients) that collects information on a drug's safety and effectiveness using different populations and different dosages, and by comparing it to other known drugs for a condition.

Phase 4 Trial

Trial conducted once a drug has been granted a licence to find out more about a drug's side effects, its long-term risks and benefits, or how well it works when it's used more widely.

Platelets

One of the types of blood cell which helps to stop bleeding.

Prognosis

Indication of how well a patient is expected to respond to treatment based on their individual characteristics at the time of diagnosis or other timepoint in the disease.

Protein Kinase Inhibitor

Protein kinase inhibitors block the protein kinase enzymes that are involved with cell growth, thereby preventing the growth of the cancer cells.

Refractory

Refractory CLL occurs when the cancer has not responded to first-line treatment.

Relapse

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.

Remission

Remission occurs when the following conditions are met:

- Blood cell counts returned to normal
- Less than 5% of blasts (early stem cells) are still present in the bone marrow
- There is no leukaemia present elsewhere in the body (minimal residual disease)

Salvage Chemotherapy

Chemotherapy given to a patient

Glossary (cont.)

when other options are exhausted.

Second-line Therapy

Treatment other than the type used the first time around (first-line treatment).

Targeted Therapy

Drugs that specifically interrupt the leukaemia cells from growing in the body. These drugs do not simultaneously harm healthy cells the way conventional chemotherapy drugs do.

Thrombocytopenia

Low levels of platelets, which are small blood cells that help the body form clots to prevent or stop bleeding.

Toxicity

Harmful effect.

Tell us what you think!

If you would like to give us some feedback about this patient information booklet, please hover over the code to the right using your phone or tablet's camera. Click the link as it appears and this will take you to a short web form to fill in.

Suitable for Android, iPhone 7 and above.

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.

Leukaemia Care

We are a charity dedicated to supporting anyone affected by the diagnosis of any blood cancer. We provide emotional support through a range of support services including a helpline, patient and carer conferences, support group, informative website, one-to-one buddy service and high-quality patient information. We also have a nurse on our help line for any medical queries relating to your diagnosis.

Helpline: **08088 010 444**
www.leukaemiacare.org.uk
support@leukaemiacare.org.uk

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.leukaemiacare.org.uk

support@leukaemiacare.org.uk

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

Registered charity
259483 and SC039207

Leukaemia Care
YOUR Blood Cancer Charity

Health & care information you can trust
The Information Standard Certified Member