Relapse in Acute Lymphoblastic Leukaemia (ALL)

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 acute lymphoblastic leukaemia (ALL).

The booklet was written by our Patient Information Writer, Isabelle Leach, and peer reviewed by Dr. Richard Kaczmarski at The Hillington Hospital NHS Foundation Trust, Dr Mark Mansour at University College of London Cancer Institute and Dr David O'Connor at GOSH. We are also grateful to our reviewer, Kerri Baker, whose son had a relapse in ALL, for their contribution.

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

Nurse service

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

Patient Information Booklets

We have a number of patient information booklets like this available to anyone who has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be found on our website at **www.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**, as well as speak to one of our care advisers on our online support service, LiveChat (9am-5pm weekdays).

Campaigning and Advocacy

Leukaemia Care is involved in campaigning for patient well-being, NHS funding and drug and treatment availability. If you would like an update on any of the work we are currently doing or want to know how to get involved, email **advocacy@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 Acute Lymphoblastic Leukaemia?

In acute lymphoblastic leukaemia (ALL), high numbers of abnormal, immature lymphocytes called blasts start over-multiplying in the bone marrow. Lymphocytes are white blood cells involved in the immune response. There are two types of lymphocytes:

1. B-cells (formed in the bone marrow) which produce antibodies that seek out and immobilise bacteria, viruses, and toxins which invade the body.
2. T-cells (formed in the thymus gland, behind the sternum) which destroy the invading organisms that have been tagged by the B-cells as well as any cells that have become cancerous.

ALL has different rates of occurrence, survival and type of lymphocytes involved in children and adults:

- Approximately 50% of patients with ALL are children under 15 years of age (with a peak from two to five years of age), and the remaining 15% of ALL cases are adults, mainly aged over 50 years.
- Five-year survival is approximately 90% in children, but only 30% to 40% in adults and elderly patients.

In children with ALL:

- 80% to 85% of ALL consists of early B-cells (also called precursor B-cell)
- 15% are early T-cells
- Approximately 2% are mature B-cells

In adults with ALL:

- 75% of cases are early B-cells
- 25% are malignant early T-cells

Prognostic risk factors

Prognostic risk factors at initial presentation, which can also be used to inidicate a poor outcome or the chances of a relapse occurring, include:

- Age at diagnosis: younger than 6 months and older than 60 years
- Male sex, possibly because of the impact of a major relapse site being in the testicles
- High white blood cell count of

greater than 300,000 white blood cells x 106 cells/L

- T-cell lymphocyte ALL rather than B-cell lymphocyte ALL
- Spread of ALL to the central nervous system (CNS)

Certain abnormal gene rearrangements can also act as prognostic risk factors. These include:

- t(9;22) BCR-ABL1 (Philadelphia chromosome)
- MLL (KMT2A) translocations
- t(17;19) TCF3-HLF
- Near haploidy (24-30 chromosomes). Haploidy is having only half of the normal number of 46 chromosomes
- Low hypodiploidy (31–39 chromosomes). Hypodiploidy is having less than the normal number of 46 chromosomes

What is a relapse?

What is a relapse?

Relapse in ALL is the return of ALL in patients who have already undergone treatment and reached complete remission.

For complete remission to have occurred, the following conditions will 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

When a relapse occurs, as with newly-diagnosed ALL, the blasts, which begin in the bone marrow, start over-multiplying again, reaching high levels beyond levels considered appropriate for remission. This is also called a recurrence.

While a large number of patients go into remission after induction therapy, there are subsets of patients who do not at all, and still have numerous blast cells in their bone marrow after treatment. This is called refractory ALL.

Between 10% and 20% of patients, who have achieved complete remission after initial treatment for ALL, will have a relapse. In children, the relapse rate is near to 10%, while in adults relapse rate is closer to 50%. Relapse of ALL generally occurs within two years of initial treatment, although it may occur several months to years after the initial remission.

Why does relapse happen?

Patients with ALL are known to have a number of characteristics that make them more likely to relapse. Patients with a likelihood or risk that they will have a relapse after treatment can be subdivided into well-defined risk groups according to these characteristics.

By way of an example, there is a well-established risk stratification for ALL patients, which is used by many doctors, shown below. This risk stratification is for children since the majority of patients with

ALL are children.

National Cancer Institute/Rome criteria for children

The National Cancer Institute/ Rome criteria uses only patients' ages and white blood cell counts to determine their risk, and predict relapse and outcome.

Standard risk - Both of the following criteria must be present:

- White blood cell count less than 50 x 109 cells/L
- Age of patient between one and nine years

High risk - Both of the following criteria must be present:

- White blood cell count greater than 50 x 109 cells/L
- Age of patient younger than one year or older than nine years

Since this risk classification was established, numerous other risks factors for relapse have been found, none more so than the implications of faulty chromosomes and genes.

Chromosomes are thread-like structures which carry the genes and are located in the nuclei of every cell. Genes are made up of DNA (deoxyribonucleic acid) which stores the genetic information required to make human proteins.

The presence of abnormal gene rearrangements alone cannot predict a relapse rate in patients, but the relationship between genetic rearrangements and the prognosis of the first occurrence of ALL can.

How often does relapse occur?

Despite the fact that around 85% of cases of ALL occur in children, its presence in the remaining 15% of adults who get ALL carries a much more serious prognosis than the children.

In children, although complete remission occurs in 97 to 99% of patients following initial multi-agent chemotherapy treatment, between 15 and 20% will have a relapse.

In adults, despite complete

What is a relapse? (cont.)

remission rates of between 78% and 93%, relapse will occur in 60-70% of patients.

In addition to different rates of relapse for ALL patients according to their age at diagnosis, other prognostic factors at initial presentation can also indicate those patients where relapse occurs more often.

Although not having any of the prognostic risk factors at initial presentation predicts less chance of relapse and a better outcome, there is always a risk of relapse irrespective of a patient's age or prognostic factors.

Symptoms and diagnosis of relapsed ALL

What are the symptoms of relapsed ALL?

The symptoms of relapsed ALL are the same as those for newly diagnosed ALL, and include:

- Anaemia
- Bruising or petechiae (small red spots on the skin)
- Fever
- Recurrent infections
- Abdominal pain
- Bone and joint pain
- Swollen lymph nodes (showing up as lumps and bumps on your neck, armpits and groin)
- Dyspnoea (difficulty in breathing)

How is relapsed ALL diagnosed?

To make a diagnosis of relapsed ALL, your doctor will carry out the following tests:

Full blood count (FBC)

This will show the number of red blood cells, white blood cells and platelets. In a relapse, ALL patients have lower-than-expected red blood cells and platelets.

A peripheral blood smear

A sample of blood is viewed under a microscope to count different circulating blood cells and to see whether the cells look normal. In relapsed ALL patients, there are too many blast cells.

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, to remove a sample from the hip bone. The following can be examined:

- Percentage of ALL cells are in your bone marrow
- Any abnormalities of the ALL cells

Immunophenotyping

This procedure identifies the types of proteins on the surface of the cell to find out if the ALL cells are B-cells or T-cells.

Lumbar puncture

This will determine if the ALL cells are in your CNS.

Chromosomal analysis (also called cytogenetic analysis)

The blood smear sample can also be used to identify certain changes in the number and size of chromosomes within cells that might have led to the relapse.

Other tests and scans

X-rays are used to monitor the presence of ALL in any organs.

How is relapsed ALL treated?

Patients with relapsed ALL remain curable despite the failure of the initial course of treatment. The treatment strategies for adult patients with ALL are similar to those for children with ALL.

The mainstay of the treatment for relapse ALL is chemotherapy, often given with steroids to improve the effectiveness. If required, novel target therapy drugs which attack specific components of the leukaemia cells can be given. High-risk patients are frequently offered an allogeneic stem cell transplant (ASCT) because the likelihood of a cure with chemotherapy alone is very low.

Chemotherapy

Chemotherapy for ALL normally consists of induction, consolidation, and long-term maintenance therapy, with CNS prophylaxis treatment to prevent blast cells entering the brain or spinal cord, often given during the first year of treatment.

After a first relapse, patients should receive re-induction therapy to try and achieve another complete remission. The treatment of relapsed ALL is normally more intensive than for newly diagnosed ALL. Treatment outcome depends on the time of the patient's relapse and the type of ALL:

- For patients who relapse during, or just after finishing chemotherapy, another course of chemotherapy is unlikely to achieve a cure. An ASCT in the second remission period is the only way to cure these patients with ALL, and should be the main focus whenever possible.
- For patients who relapse six months or longer after finishing treatment, many patients can achieve a second remission with therapy similar to that used in initial treatment.
- For patients with B-cell ALL with a late first bone marrow relapse and low levels of MRD, chemotherapy can achieve a positive outcome. In addition, the dual specific antibody, blinatumumab, is known to inactivate the T-cell immune response against B-cells and

directly activate T-cells against the ALL blasts. Blinatumumab is recommended by the National Institute for Health and Care Excellence (NICE) as an option for treating Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL in adults. A recent study of 113 adults with B-cell precursor ALL in complete haematological remission showed that blinatumumab achieved a complete MRD response in 78% of patients. However, an ASCT, particularly for those patients with unfavourable genetic factors and/or who are MRD-positive, offers a significant benefit.

- For patients with T-cell ALL, intensive multi-agent chemotherapy can achieve good outcomes.

Discovery of abnormal gene rearrangements in patients with ALL will also influence the choice of treatment. The Philadelphia chromosome (BCR-ABL) is the most common genetic abnormality associated with adult ALL and has a very poor prognosis for both children and adults. It only occurs in 3% to 5% of patients with ALL, but less than 40% of them are cured with intensive chemotherapy.

A young person who is Philadelphia chromosome-positive will be a candidate for an ASCT in the first remission. Patients who relapse but achieve a second complete remission may also benefit from an ASCT. However, the success of tyrosine kinase inhibitors in chronic myeloid leukaemia (CML) has encouraged their use in Philadelphia chromosome-positive ALL patients. The tyrosine kinase inhibitor, imatinib, has achieved complete remission rates of 90%-100% for patients who have Philadelphia chromosome-positive ALL with relatively low toxicity. However, the combination of a tyrosine kinase inhibitor with standard chemotherapy has led to a longer survival in both adults and children.

Relapses can result from a lack of response to standard chemotherapy agents. In patients

How is relapsed ALL treated? (cont.)

with refractory ALL, or patients who have had several relapses, multidrug treatment is often used with the aim of eliminating blast cells and targeting therapy-resistant cells that could cause further episodes of relapse.

Introduction of new treatments from trials for high-risk patients is an option for improving outcome. Other possibilities which can also be explored include the following:

- Ground-breaking combinations of chemotherapy drugs
- Antibodies directed against the leukaemia
- Drugs that stimulate the body's immune system to attack the leukaemia

Chimeric Antigen Receptor (CAR) T-cell therapy:

This new cancer treatment works by removing the patient's own immune cells, genetically modifying them to recognise the tumour cells, and then re-infusing them back into the patient so they can target the cancer cells.

Clinical trials of CAR T-cell therapy for relapsed or refractory B-cell cancers, such as B-cell leukaemia and lymphoma, and several solid tumors, have shown promising results. The anti-CD19 CAR T-cell therapy has achieved remission in up to 90% of patients with B-cell ALL. CD19 is a B-cell receptor associated protein present on the surface of B-cells. However, relapse after CAR T-cell therapy is still a problem, often because the ALL cells lose expression of CD19.

The anti-CD19 agent tisagenlecleucel (Kymriah) is the first CAR T-cell therapy to be approved in the United States for the treatment of patients up to 25 years of age with B-cell ALL that is refractory or in second or later relapse. In Europe, this anti-CD19 CAR T-cell drug has been approved by the European Medicines Agency and NICE.

Chemotherapy for T-cell ALL, paying special attention to the patient's responses to previous treatments, has also resulted in good survival rates. Patients with mature T-cell ALL have a better outcome than those with early

T-cell ALL.

A major challenge in the future treatment of ALL will be to devise less toxic regimens for patients with low-risk disease and high cure potential, with the ultimate goal of improving their quality of life.

Allogeneic stem cell transplantation

High-risk patients are frequently offered an ASCT because the likelihood of a cure with chemotherapy alone is very low. Currently an ASCT is an established treatment for high-risk acute leukaemia.

Patients who have a bone marrow relapse following initial chemotherapy treatment may benefit from a stem cell transplant (SCT); however, this is not uniformly recommended. General procedure for ASCT in ALL patients involves total body irradiation, because outcomes are improved in patients who undergo transplant after achieving a low MRD status.

Careful selection of SCT for ALL patients is important to achieve the best outcomes. Human leukocyte antigen (HLA)-matched sibling donors are recognised as the best option, but this is only available for 30% of patients. Alternative sources of stem cells for the remaining 70% of patients include matched unrelated adult volunteer donor, a haploidentical donor or a cord blood unit.

ASCTs are increasingly performed due to the improved availability of alternative donors and refinement of indications according to the NHS England Clinical Commissioning Policy for Haematopoietic Stem Cell Transplantation. In addition, the advent of the haploidentical stem cell transplantation (HID-SCT), where the donor matches exactly half of the HLA, offers another option for patients, although this option only accounts for approximately 10% of ASCTs in the UK.

Adults with Philadelphia chromosome-negative ALL in their first complete remission

How is relapsed ALL treated? (cont.)

will benefit from an HLA-matched donor ASCT or a HID-SCT. Moreover, children with T-cell ALL benefit from ASCTs, including HID-SCT.

Philadelphia chromosome-positive ALL patients who have received a HLA-matched donor ASCT compared to those who had a HID-SCT showed similar results in studies with children and adults. In a study of 82 Philadelphia chromosome-positive ALL Chinese patients, HID-SCT was associated with a meaningful lower relapse rate compared with HLA-matched donor ASCT (44.8 vs. 19.1%, respectively), although overall survival times were the same.

If an HLA-identical sibling donor is not available, the probability of finding a fully matched unrelated donor should be estimated to help inform the decision on whether to search for an unrelated donor or find an alternative source of haematopoietic stem cells (haploidentical donor or cord blood unit).

Prognosis

Adults with ALL who relapse have a poor prognosis. Young adults less than 30 years old with a first complete remission of two years or more may have the chance of long-term survival; however, older patients (>30 years) who relapse early do not have realistic survival options with current therapies.

Despite the great improvements in the treatment of ALL in children, with a five-year overall survival of approximately 90%, the prognosis is still much lower for children who have relapsed, compared with newly diagnosed ALL.

If you would like some support or advice about your relapse, you can speak to the Patient Advocacy team by calling **08088 010 444** or emailing **support@leukaemiacare.org.uk**

Glossary

Allogeneic Stem Cell Transplant

Transplant of stem cells from a matching donor.

Antibody

Blood protein produced by the B-cell lymphocytes in response to, and counteracting, a specific antigen such as a bacteria, virus, or foreign substance.

Autologous Stem Cell Transplant

Transplant of stem cells derived from part of the same individual.

Blasts

These white blood cells are not fully developed and are called blasts or leukaemia cells.

Bone Marrow Relapse

Bone marrow relapse is defined as the presence of 25% of lymphoblasts or more in a bone marrow aspirate following the first complete remission.

Central Nervous System (CNS)

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 include an individual's genes, and are located in the nuclei of every cell in the body. There are 46 chromosomes (23 pairs) in humans.

CNS3 status

CNS3 status occurs when the cerebrospinal fluid sample contains equal to or greater than 5 white blood cells/µL with identifiable blasts, or there is the presence of a cerebral (brain) mass or cranial palsy.

Complete Remission

Complete remission occurs 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

Cranial Nerve Palsy

Weakness and impaired function (palsy) of one or more of the twelve cranial nerves caused by tumours, trauma, impaired blood flow, and infections. The condition may also be congenital.

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.

Genes

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

Haploidentical Stem Cell Transplantation (HID-SCT)

Type of allogeneic transplant of stem cells where the donor matches exactly half of the human leukocyte antigens.

Leukaemia

A group of cancers that usually begin in the bone marrow and result in high numbers of abnormal white blood cells known as blasts.

Hypodiploidy

Hypodiploidy is having less than the normal number of 46 chromosomes.

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 if infection or cancer occurs. Lymph nodes 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.

Petechiae

Red or purple, flat, pinhead spots under the skin.

Philadelphia chromosome (BCR-ABL1)

BCR-ABL1 is a cancer gene formed

Glossary (cont.)

by the fusion of chromosomes 9 and 22 [t(9;22) (q34;q11)]. BCR-ABL1 is found in all patients with chronic myeloid leukaemia and some patients with ALL.

Platelets

Platelets are one of the types of blood cells which help to stop bleeding.

Precursor Cell

Precursor cells are a type of partially differentiated stem cell which has the capacity to differentiate into only one cell type (B-cell or T-cell).

Refractory (leukaemia)

Refractory leukaemia is a leukaemia that does not result in a remission or that gets worse within six months of the last treatment. However, the leukaemia may be stable.

Relapse

A relapse is when a patient initially responds to therapy but, after six months or more, response stops. This is also sometimes called a recurrence.

Thymus Gland

Main organ of the lymphatic system, located behind the sternum and between the lungs, where the T-cell lymphocytes develop and mature.

Tyrosine Kinase Receptors

Receptors present in the membranes of all of the body's cells which contain the enzyme tyrosine kinase that carries information to and from complex cell networks. It functions as an 'on' or 'off' switch in many cellular functions.

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**

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Leukaemia Care
YOUR Blood Cancer Charity

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