
Richter Syndrome in Chronic Lymphocytic Leukaemia (CLL)

**A Guide for
Patients**

Leukaemia Care
YOUR Blood Cancer Charity

Introduction

This booklet covers Richter syndrome (RS), also called Richter transformation, which is the development of an aggressive lymphoma in patients with chronic lymphocytic leukaemia (CLL). If you have questions about Richter syndrome – 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.

If you would like specific, tailored advice, speak to your medical team or your GP.

This booklet was written by our Patient Information Writer, Isabelle Leach and peer reviewed by Professor Chris Fegan. We are also grateful for Sharon Walker's contribution as a patient reviewer.

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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About Leukaemia Care

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

Our services

Helpline

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

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

Nurse service

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

Patient Information Booklets

We have a number of patient information booklets like this available to anyone who

has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be found on our website at **www.leukaemicare.org.uk/support-and-information/help-and-resources/information-booklets/**

Support Groups

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

Buddy Support

We offer one-to-one phone support with volunteers who have had blood cancer themselves or been affected by it in some

way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call **08088 010 444** or email **support@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: **www.leukaemiacare.org.uk/communication-preferences/**

What is Richter syndrome?

There are three types of lymphocytes:

- 1.** B-cells produce antibodies and seek out and immobilise bacteria, viruses, and toxins in the body.
- 2.** T-cells destroy invading organisms that have been labelled with an antibody by the B-cells, as well as cells that have become virally infected or cancerous.
- 3.** NK-cells (natural killer cells) attack cancer cells and viruses.

Chronic Lymphocytic Leukaemia (CLL) is a cancer of the B-lymphocyte cells (B-cells).

If you wish to have further information on CLL please view our collection of patient information booklets that are available on our website at www.leukaemiacare.org.uk

Richter syndrome (RS), also called Richter transformation, is the development of an aggressive lymphoma in patients with chronic lymphocytic leukaemia (CLL).

Richter syndrome can affect around 0.5% of all CLL patients per annum giving an overall risk of 10–15%.

There are two types of Richter syndrome:

- 4. Diffuse large B-cell lymphoma (DLBCL-type RS)** – about 90% of RS cases
- 5. Hodgkin lymphoma (HL-type RS)** – about 10% of RS cases

Richter syndrome can occur any time after the diagnosis of CLL, even in patients who have never required treatment for their CLL.

In DLBCL-type RS, around 80% are related to the underlying CLL (clonally related). This means they have evolved from the CLL cells into DLBCL. To contrast, in around 20% of DLBCL-type RS and HL-type RS, these appear completely unrelated (clonally unrelated)

to the CLL. With this, the Richter syndrome is presumed to be a new tumour developing in that patient. Although the exact reasons why some CLL patients can develop a completely unrelated DLBCL-type RS and HL-type RS are unknown, it is known that some genetic abnormalities seen in CLL patients can predispose to other B-cell tumours including Hodgkin Lymphoma. This is also a type of B-cell tumour characterised by the presence of multi-nucleated Reed-Sternberg cells.

Risk factors for developing Richter syndrome

The reasons why a small minority of CLL patients develop Richter syndrome are presently unknown. However, we do know that certain abnormalities identifiable within the CLL cells predispose to Richter syndrome.

IGVH gene usage

IGVH-mutation status is a very well known prognostic marker in CLL; whether someone has mutated or unmutated VH genes. However, there are very many types - over 200 - of IGVH genes identified in CLL patients and one, IGVH 4-39, is associated with DLBCL-type RS.

Genetic abnormalities

About 30% of DLBCL-type RS patients have mutations in the NOTCH 1 gene and we know that around 3% of CLL patients have the same genetic abnormalities at diagnosis. NOTCH 1 mutations, which are themselves more common in patients with an extra chromosome 12 (trisomy 12) at CLL diagnosis, are probably a risk factor. NOTCH 1 is a regulator of a gene very important in B-cell development called MYC and

abnormalities in this gene occur in about 40% of Richter syndrome patients. Likewise, we know that TP53 dysfunction and a complex genetic pattern (karyotype) also pre-dispose to DLBCL-type RS. Presumably, this is due to the inherent instability of the genome in these situations giving rise to new genetic abnormalities in NOTCH 1, MYC or other genes such as CDKN2A. There is evidence that patients with the triad of trisomy 12, NOTCH 1 and IGVH 4-39 are especially prone to developing DLBCL-type RS.

Previous CLL Treatment

Previously there were suggestions that prior chemotherapy or antibody therapy either protected or increased the risk of Richter syndrome but this is now not thought to be correct. However, the newer non-chemotherapy/antibody agents, including ibrutinib, idelalisib and venetoclax, have been associated with the development of Richter syndrome usually within two years of commencing treatment with these agents. Indeed, in the very early ibrutinib studies, 5-10%

of patients developed Richter syndrome. However, later studies - especially in those patients who were not as heavily pre-treated as those in the early ibrutinib studies - suggest the risk is much lower. This data suggests that very heavily pretreated CLL patients, who have almost exhausted all therapeutic options with chemotherapy and antibody agents, have pre-existing but clonally related Richter cells which ibrutinib selects for.

Historically there were reports suggesting that some infective agents such as the Epstein-Barr virus (EBV) play a role in the development of Richter syndrome. However, this is no longer thought to be the case as the overwhelming majority of DLBCL-type RS are EBV negative whilst it may be positive in HL-type RS. Given its rarity, very little else is known about risk factors in HL-type RS.

Signs and symptoms

The median age of patients who develop Richter syndrome in CLL is around 66 years. As is the case with CLL, the incidence of Richter syndrome is twice as common in men compared with women.

The signs and symptoms associated with the development of DLBCL-type RS and HL-type RS are:

- High-grade fever (39.4°C to 40°C) in the absence of obvious infection
- Chills and rigors
- Night sweats
- Weight loss
- Rapid or asymmetrical growth of lymph nodes
- Rapidly enlarging liver and/or spleen
- Apparent spread of disease outside of lymphoid tissue areas
- Significantly increased and rapidly rising blood lactate dehydrogenase levels
- Hypercalcaemia (increased levels

of calcium in the blood)

- Dysfunction of many body organs

Diagnosis

The clinical suspicion of Richter syndrome should be based on signs and symptoms. Richter syndrome progresses rapidly with the enlargement of localised or widespread increase in lymph nodes and possible involvement in other organs.

The development of Richter syndrome in patients with CLL may be mistaken for a worsening of the CLL. Therefore, it is important to establish if the CLL is actually progressing or if a Richter transformation is occurring. This will impact on the treatment received.

The diagnosis of Richter syndrome usually requires a tissue biopsy of either a sample of a lymph node or bone marrow. Occasionally Richter lymphoma cells circulate in the blood and a blood film and a special blood test called immunophenotyping may be adequate to make the diagnosis. Often, the expression of proteins normally expressed on CLL cells e.g. CD5, CD20, CD23 reduces or disappears completely.

As Richter syndrome is a much more rapidly growing disease than CLL, a positron emission

tomography (PET) scan can provide very useful information including:

- Distinguishing Richter syndrome from advanced and possibly rapidly growing CLL
- Identifying the best site for taking a biopsy for histological confirmation.
- Determine the extent (staging) of Richter syndrome within a patient.

Following the diagnosis of Richter syndrome by tissue biopsy, a bone marrow aspirate and biopsy are performed to complete the disease staging and identify any of the possible genetic lesions that may have led to the development of Richter syndrome.

Richter syndrome rarely involves the central nervous system (part of the nervous system that includes the brain and spinal cord). Therefore, investigations such as lumbar puncture and magnetic resonance imaging of the head are only performed in patients with DLBCL-type RS if there is evidence of spread outside lymphoid tissue.

Prognosis

The clonal relationship between the CLL and DLBCL is very important as clonally unrelated DLBCL-type RS has an average survival of around five years compared to only 12 to 18 months in the clonally related DLBCL-type RS, which may be even shorter for those patients who develop Richter syndrome whilst receiving ibrutinib or venetoclax.

HL-type RS has traditionally been treated in the same way as Hodgkin Lymphoma but has a lower response rate of 40-60% and an average survival of around four years.

Prognostic factors

DLBCL-type RS

In patients with DLBCL-type RS, risks factors which are associated with a shorter overall survival include:

- Eastern Cooperative Oncology Group (ECOG) performance status >1
- Haemoglobin level <10g/dL
- Platelet count <100 x 10⁹/L

- Lactate dehydrogenase levels >1.5 x upper normal limit
- 2-microglobulin >3mg/dL
- More than one prior therapy for CLL
- Presence of the TP53 dysfunction

HL-type RS

In patients with HL-type RS, advanced age is also a risk factor for poor survival.

Prognostic scores

Prognostic scores for Richter syndrome patients have been developed to predict the outcomes in patients treated with chemotherapy or chemoimmunotherapy.

These prognostic scores include specific Richter syndrome scoring systems and the International Prognostic Index scoring systems for DLBCL and Hodgkin Lymphoma. The International Prognostic Index score was devised to predict the outcome of patients with DLBCL in general, and is not specific for patients with DLBCL-type RS, although its

accuracy for clonally unrelated DLBCL-type RS is thought to be the same as for DLBCL.

A validated Richter syndrome prognostic score is based on the following five adverse risk factors:

- ECOG performance status 0 or 1
- Elevated Lactate dehydrogenase levels $>1.5 \times$ upper normal limit
- Platelet count $\leq 100 \times 10^9/L$
- Lymphoma tumour $\geq 5\text{cm}$ in diameter
- Number of prior therapies for CLL >2

Patients were assigned one point for each adverse characteristic and their risk classified as follows based on their total score:

- **Score 0 to 1:** good prognosis - low risk
- **Score 2:** good prognosis - low-intermediate risk
- **Score 3:** poor prognosis - high-intermediate risk
- **Score 4 to 5:** poor prognosis - high risk

However, the clonal relationship between the original CLL and the DLBCL-type RS is the most important prognostic factor.

Treatment

DLBCL-type RS

DLBCL is much more common than DLBCL-type RS and hence the treatment of DLBCL-type RS is presently identical, typically using a combination of various chemotherapy agents and monoclonal antibodies. The most commonly used regimen is R-CHOP which consists of rituximab, cyclophosphamide, adriamycin, vincristine and prednisolone - so-called chemo-immunotherapy as they include a combination of chemotherapy and immunotherapy agents. As the prognosis of clonally unrelated DLBCL-type RS is indistinguishable from DLBCL, R-CHOP alone may cure around 50% with stem cell transplantation being reserved for those whose Richter syndrome relapses after R-CHOP. However, given the poorer outlook in clonally related DLBCL-type RS, many patients proceed straight to an autologous (using the patient's own stem cells) or allogeneic (using a donor's stem cells) transplant.

The decision as to whether to use autologous or allogeneic transplant depends on:

- The general health of the patient
- The response to the initial Richter syndrome chemoimmunotherapy
- The availability of a suitable allogeneic donor
- The clonal relationship between the original CLL and the Richter syndrome cells

A large European study reported that 36% of allogeneic transplant and 59% of autologous transplant Richter syndrome patients were alive at three years with all transplant patients having a better outlook if the Richter syndrome is in remission at the time of transplant and, in the allogeneic setting, patients aged less than 60 years do better.

To try and improve the overall outcome, much more intensive chemoimmunotherapy regimens have been used to treat Richter syndrome, including adding drugs such as etoposide, cisplatin, fludarabine, methotrexate and

cytosine arabinoside, but at present no alternative regimen has been shown to be consistently superior to R-CHOP.

HL-type RS

Given the excellent responses achievable in Hodgkin Lymphoma, the same chemotherapy consisting of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) is the standard of care treatment for HL-type RS.

An autologous or allogeneic haematopoietic stem cell transplant is reserved for those who relapse.

Some of the new immunotherapies used for treating patients with Hodgkin Lymphoma may be helpful for HL-type RS patients who relapse, including the monoclonal antibody brentuximab vedotin, which is an antibody linked to the drug monomethyl auristatin E directly killing Hodgkin cells, and pembrolizumab and nivolumab monoclonal antibodies which block a protein called PD-1 which

enables a patient's own immune system to kill tumour cells.

Clinical trials

The treatment of CLL has changed enormously in the last five years and many of these new agents are now being tested usually in combination with chemoimmunotherapy or with each other in clinical trials in Richter syndrome including:

- Monoclonal antibodies (obinutuzumab, ofatumumab, ublituximab, blinatumomab, nivolumab and pembrolizumab)
- B-cell receptor inhibitors (ibrutinib, acalabrutinib and umbralisib)
- PI-3 Kinase inhibitor (duvelisib)
- BCL-2 inhibitor (venetoclax)
- Nuclear export inhibitor (selinexor)

Details of these trials and other trials can be found on the ClinicalTrials.gov website.

Glossary

Allogeneic stem cell transplantation (ASCT)

The transplant of stem cells from a donor which may or may not be related to the patient.

Antibody

A large Y-shaped protein produced by B-cell lymphocytes in response to a specific antigen, such as a bacteria, virus, or a foreign substance in the blood. The antibodies neutralise bacteria and viruses.

Antigen

A toxin or other foreign substance or protein which induces an immune response in the body.

BCL-2

BCL-2 proteins are large proteins that are involved in the process of natural programmed cell death. Cell death is an active process via stimulation of specific signalling pathways often triggered when cells have become damaged or abnormal.

B-cell receptor

A receptor located on the outer surface of the B-lymphocyte. The B-cell receptor activates B-cells by biochemical signalling leading to cell survival pathways being activated.

Beta 2 microglobulin

A small protein found on the surface of most cells in the body, which shed into the blood, particularly by B-cells and tumour cells. It can be used to assess the severity of certain cancers, including multiple myeloma and some lymphomas.

Bone marrow

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

Bone marrow aspirate

The process of taking a sample of the liquid part of the soft tissue bone marrow inside the bones using a special needle and syringe.

Bone marrow biopsy

A bone marrow biopsy involves the collection of a sample of bone marrow from the hip bone, generally under local anaesthesia. A bone marrow surgical instrument with a cylindrical blade, called a trephine biopsy needle, is used to remove a 1-2cm core of bone marrow.

CDKN2A gene

A gene that provides instructions for making several proteins,

including tumour suppressing proteins, which prevent cells from growing and dividing too rapidly or in an uncontrolled way.

Chemotherapy

Drugs that stop the growth of cancer cells, either by killing the cells or by stopping them from dividing.

Chemoimmunotherapy

Chemotherapy combined with immunotherapy. The chemotherapy kills or slows the growth of cancer cells and the immunotherapy can either directly kill tumour cells or stimulate the body's own immune system to fight cancer cells.

Chromosomes

Made up of DNA, these are X-shaped, 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 approximately 276,190 research studies in 205 countries.

DNA (deoxyribonucleic acid)

The thread-like chain of nucleic acids found in the nucleus of

each cell in the body which carries genetic instructions used to produce protein involved in the growth, development and normal functioning of cells.

Eastern Cooperative Oncology Group (ECOG) performance status

The ECOG performance status is a scale used to assess the daily living abilities of the patient.

Epstein-Barr virus

This virus is responsible for infectious mononucleosis (glandular fever).

Genes

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

Gene mutation

The small-scale alteration of the genetic material, which primarily is a change in one of the building blocks of the gene's DNA.

Hypercalcemia

A condition in which calcium levels in the blood are increased.

Immunoglobulin variable region heavy chain (IgVH) gene

A gene which allows mature B-cells to vary the antibodies they produce. In CLL, patients who

Glossary (cont.)

have mutated IgVH genes have a better prognosis than those with unmutated IgVH genes.

Lactate dehydrogenase

An enzyme that is required during the process of turning glucose (sugar) into energy for the body cells. It is often elevated in fast growing lymphomas and leukaemias.

Ligand

A protein which produces a signal by binding to a site on a target protein.

Lymphoma

A cancer of the lymphocytes which usually reside in the lymph nodes, spleen, liver, bone marrow, and occasionally other parts of the body.

MYC gene

A gene that plays a role in how the cell cycle progresses, the transformation of cells and programmed cell death.

NOTCH1 (Neurogenic locus notch homologue protein 1) gene

A gene involved in the control of the fate of the cells of the body.

Platelets

Small blood cells that help the body form clots to stop bleeding.

Positron emission tomography (PET) Scan

A scan which uses small amounts of radioactive materials, a special camera and a computer to help assess the organs and tissues of the body. By identifying body changes at the cell level, PET scans detect the early onset of disease before it can be seen by other imaging tests.

Prognosis

An indication of how well a patient is expected to do either with or without treatment.

Programmed death 1 (PD-1)

A key receptor in the immune system which is involved with activated T-cells, B-cells and NK-cells.

Reed-Sternberg cells

Giant cells with several nuclei that are a characteristic feature of Hodgkin lymphoma.

Spleen

The largest organ of the lymphatic system whose function is to help rid the body of toxins, waste and exhausted blood cells. The spleen is located under the ribs on the left of the abdomen.

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.

Helpline: **08088 010 444**

www.leukaemiacare.org.uk
support@leukaemiacare.org.uk

CLL Support

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

www.clisupport.org.uk

0800 977 4396

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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