

# Cancer Association of South Africa (CANSA)



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## Fact Sheet on Richter's Syndrome

### Introduction

The non-Hodgkin lymphomas (NHLs) are a diverse group of blood cancers that include all kinds of lymphoma except Hodgkin's lymphomas. Types of NHL vary significantly in their severity, from slow growing to very aggressive types.

[Picture Credit: Richter's Syndrome]

Lymphomas are types of cancer derived from lymphocytes, a type of white blood cell. Lymphomas may be treated by combinations of chemotherapy, monoclonal antibodies (CD20), immunotherapy, radiation, and haematopoietic stem cell transplantation.



The 2008 the World Health Organization (WHO) classification of lymphomas has five large groups, including a Hodgkin disease group. Other forms of lymphoma include over 80 different forms of lymphoma in an additional four broad groups. By comparison, the 1982 Working Formation (which is now considered obsolete, is commonly used primarily for statistical comparisons with previous decades) recognised just 16 types of non-Hodgkin lymphoma.

Richter's syndrome is a type of high grade non-Hodgkin's Lymphoma. It is a diffuse large B cell lymphoma. It is called diffuse because of the way the cells look under a microscope. 'Diffuse' means spread out.

### Richter's Syndrome

Richter's syndrome is very rare. It starts as chronic lymphocytic leukaemia (CLL). Then sometimes the leukaemia cells get into the lymph nodes and start growing there. In the advanced stage CLL can change and become Richter's syndrome. Fewer than 5 out of every 100 people with CLL develop Richter's syndrome. It is a quickly developing cancer. People with Richter's Syndrome can become

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April 2020

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unwell quite suddenly. CLL (chronic lymphocytic leukaemia) and SLL (small lymphocytic lymphoma) are the same disease, but in CLL cancer cells are found mostly in the blood and bone marrow. In SLL cancer cells are found mostly in the lymph nodes.

Richter's Syndrome (RS), also known as *Richter's Transformation*, is characterised by the sudden transformation of the CLL/SLL into a significantly more aggressive form of large cell lymphoma. Richter's Syndrome occurs in approximately 2-10% of all CLL/SLL patients during the course of their disease. In the most cases it is normally slow growing, or indolent - CLL transforms into a common type of non-Hodgkin lymphoma (NHL) known as Diffuse Large B-Cell Lymphoma (DLBCL). Rarer cases transform into Hodgkin lymphoma (HL)/Hodgkin Disease (HD), and some types of T-cell lymphomas also have been reported.

**Roncati, L. 2020.**

“By definition, Richter's syndrome represents the transformation of low-grade B-cell lymphoma into high-grade B-cell lymphoma, usually refractory to treatment. Exceptional cases of transformation into very aggressive mature T-cell lymphomas have been described as an unusual manifestation of the syndrome in patients died after few months from the diagnosis, despite chemotherapy. The time is ripe to regroup these T lymphomas under a new pathological subset, through the unequivocal alternate naming of 'T rex lymphoma', by analogy with the aggressive behavior of the famous dinosaur (T. rex). In practice, it represents the transformation of low-grade B-cell lymphoma into high-grade T-cell lymphoma, burdened by a very poor prognosis, because of the underlying B-cell lymphoma, which negatively interferes with the immune response of the patient. Against this distinct lymphomatous T clone, the major therapeutic efforts should be addressed.”

**Van Roosbroeck, K., Bayraktar, R., Calin, S., Bloehdorn, J., Dragomir, M.P., Okubo, K., Bertilaccio, M.T.S., Zupo, S., You, M.J., Gaidano, G., Rossi, D., Chen, S-S., Chiorazzi, N., Thompson, P.A., Ferraioli, A., Bertoni, F., Stilgenbauer, S., Keating, M.J. & Calin, G.E. 2019.**

Richter syndrome is the name given to the transformation of the most frequent type of leukemia, chronic lymphocytic leukemia, into an aggressive lymphoma. Patients with Richter syndrome have limited response to therapies and dismal survival. The underlying mechanisms of transformation are insufficiently understood and there is a major lack of knowledge regarding the roles of microRNA that have already proven to be causative for most cases of chronic lymphocytic leukemia. Here, by using four types of genomic platforms and independent sets of patients from three institutions, we identified microRNA involved in the transformation of chronic lymphocytic leukemia to Richter syndrome. The expression signature is composed of miR-21, miR-150, miR-146b and miR-181b, with confirmed targets significantly enriched in pathways involved in cancer, immunity and inflammation. In addition, we demonstrated that genomic alterations may account for microRNA deregulation in a subset of cases of Richter syndrome. Furthermore, network analysis showed that Richter transformation leads to a complete rearrangement, resulting in a highly connected microRNA network. Functionally, ectopic overexpression of miR-21 increased proliferation of malignant B cells in multiple assays, while miR-150 and miR-26a were downregulated in a chronic lymphocytic leukemia xenogeneic mouse transplantation model. Together, our results suggest that Richter transformation is associated with significant expression and genomic loci alterations of microRNA involved in both malignancy and immunity.

## Incidence of Richter's Syndrome in South Africa

The National Cancer Registry (2014) does not furnish any information on the incidence of Richter's Syndrome in South Africa. It groups all forms of non-Hodgkin's Lymphoma together. According to the National Cancer Registry (2014) the following number of Non-Hodgkin's Lymphoma cases were histologically diagnosed in South Africa during 2014:

Group - Males 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	932	1:221	2,53%
Asian males	36	1:182	3,84%
Black males	533	1:331	4,81%
Coloured males	89	1:189	2,11%
White males	274	1:113	1,33%

Group - Females 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	870	1:296	2,30%
Asian females	39	1:206	3,28%
Black females	492	1:448	3,06%
Coloured females	91	1:205	2,22%
White females	249	1:156	1,52%

The frequency of histologically diagnosed cases of Non-Hodgkin's Lymphoma in South Africa for 2014 was as follows (National Cancer Registry, 2014):

Group - Males 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	42	53	161	219	180	143	82	33
Asian males	2	4	3	5	5	10	5	1
Black males	31	36	128	149	98	43	15	5
Coloured males	4	3	8	20	22	16	10	4
White males	2	9	15	32	38	67	55	28

Group - Females 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	22	59	168	179	115	139	104	58
Asian females	0	1	3	10	8	12	1	2
Black females	14	50	140	133	58	37	21	7
Coloured females	6	2	12	7	10	24	19	9
White females	1	4	13	22	38	63	61	39

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

## Signs and Symptoms of Richter's Syndrome

Patients may experience the following:

- Rapidly enlarging lymph nodes
- Abdominal discomfort related to enlargement of the spleen and liver (called hepatosplenomegaly)

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- Symptoms of low red blood cell count (anaemia), such as feeling extra tired, pale skin, shortness of breath
- Symptoms of low platelet count (thrombocytopenia), such as easy bruising and unexplained bleeding
- Signs of extranodal involvement in unusual sites, such as brain, skin, gastrointestinal system, skin, and lungs
- Fever which is not caused by an infection
- Night Sweats
- Weight loss

### Diagnosis of Richter's Syndrome

Most patients contact their doctor because they have developed new symptoms. The doctor will do a clinical examination and arrange for the patient to have tests similar to those for CLL.

These tests may include:

- Lymph node biopsy - to make a diagnosis of Richter's syndrome your doctor will need to take some cells from one of your enlarged lymph nodes. A pathologist will then look at the cells under a microscope. For this test you'll usually need to have one of the enlarged lymph nodes removed during a small operation, usually under general anaesthetic.
- Blood tests – the patient may have various blood tests. These include a full blood count and a test to check the patient's levels of an enzyme called lactate dehydrogenase (LDH). LDH is a normal substance in the blood, but it is at higher than normal levels in some types of cancer.

LDH levels in the blood can go up if someone has Richter's syndrome.

Other tests may include a:

- Bone marrow biopsy
- CT scan.

**Lenartova, A., Randen, U., Johannesen, T.B. & Teiønnfjord, G.E.** 2019.

**Background:** Transformation to aggressive lymphoma (Richter syndrome, RS) occurs in a substantial subset of patients who must discontinue targeted therapy for chronic lymphocytic leukemia (CLL). RS has an extremely poor prognosis.

**Methods:** Using the nation-wide database of The Cancer Registry of Norway of 7664 CLL patients registered between 1953-2012, we identified 107 patients experiencing RS.

**Results:** Seventy seven (72%) of RS patients were identified among 2631 CLL patients diagnosed between 2003-2012; diffuse large B-cell lymphoma (DLBCL) was identified in 65 (84%), Hodgkin lymphoma (HL) in 12 (16%) patients and the diagnosis was confirmed in 50 (65%) available biopsy specimens. The incidence rate in this period was 4.7/1000 person-years (95% CI: 3.8-5.9). The median survival from CLL diagnosis was 1.7 years (95% CI: 0.34-2.3) for RS patients while it was 10.3 years (95% CI: 9.5-10.9) for the remaining CLL patients. Male gender predominated among RS patients (69%) compared to CLL population (58%) and RS patients were diagnosed with CLL at a significantly younger age than the remaining patients (65 vs. 72 years). Median time from diagnosis of CLL to RS was 2 years (Range, 0-13 years). No CLL treatment was administered in 25 (33%)

patients prior RS diagnosis; a median of 1 treatment line was administered to pretreated patients. The median duration of survival after RS diagnosis was 27 months (95% CI; 9-88).

**Conclusions:** Collectively, RS was a rare complication of CLL in the chemoimmunotherapy era, occurred early in the CLL course in younger, and both treatment naïve and pretreated patients, and shortened survival substantially.

### **Treatment of Richter's Syndrome**

Treatment options for these patients are limited and include combination chemotherapy with or without the addition of monoclonal antibodies and stem cell transplantation. Response to therapy is variable and generally short-lived. Median survival is usually in the order of 5-8 mo. More effective management for RS is needed as well as prognostic models that will identify CLL patients at risk of transformation.

(Swords, *et al.*).

Chemotherapy - this is the most common treatment for Richter's syndrome. Because Richter's syndrome is similar to both acute leukaemia and lymphoma, the chemotherapy treatment may be the same as the treatment for:

- Non-Hodgkin's lymphoma (NHL)
- Acute lymphoblastic leukaemia (ALL).

Monoclonal antibodies - monoclonal antibodies (MABs) are a type of biological therapy. They are artificially made proteins that target specific proteins on cancer cells. Monoclonal antibodies are a fairly new treatment for cancer. Doctors often use the MAB drug rituximab with chemotherapy and steroids to treat Richter's syndrome. Researchers in a trial called the CHOP-OR study are looking at whether a biological therapy similar to rituximab can make CHOP chemotherapy work better. The new drug is called ofatumumab (Arzerra). The study is for people who have just been diagnosed with Richter's syndrome.

People taking part in the CHOP-OR trial have ofatumumab with CHOP chemotherapy to get rid of the lymphoma (called induction treatment). They then have more ofatumumab on its own to try to stop the lymphoma coming back (called maintenance treatment). This trial has now closed and results are awaited.

Stem cell transplant - stem cells are very early blood cells. Having a stem cell transplant means the patient receives stem cells from a donor. The person who donates the stem cells is usually a brother or sister.

First, the patient has very high doses of chemotherapy, sometimes with radiotherapy. This destroys both the cancerous and healthy cells in the bone marrow. After the chemotherapy treatment, the doctors give the patient the donor's stem cells to replace the destroyed cells.

Stem cell transplant is an experimental way of treating Richter's syndrome. While only a few people have had this treatment, for those people it appeared to work quite well. The disease was controlled for longer than for people having normal dose chemotherapy. But stem cell transplants have serious

side effects and complications, so are only suitable for a few people. More research is needed as it is too early to say how well this treatment works for Richter's syndrome.

**Radiotherapy** - radiotherapy is the use of radiation to treat cancer. The patient may have radiotherapy in combination with chemotherapy. The patient will only have radiotherapy:

- If Richter's syndrome is affecting the brain or spinal cord
- To control pain from enlarged lymph nodes

**Rossi, D.** 2016.

"Richter's syndrome (RS) is the development of an aggressive lymphoma in patients with a previous or concomitant diagnosis of chronic lymphocytic leukemia (CLL). The incidence rate for RS is ~0.5% per year of observation. In the presence of clinical suspicion of RS, diagnosis of transformation and choice of the site of biopsy may take advantage of <sup>18</sup>F PET/CT. Molecular lesions of tumor suppression regulators (TP53), cell cycle (CDKN2A) and cell proliferation (NOTCH1, MYC) overall account for ~90% of RS and may be responsible for its aggressive clinical phenotype. The prognosis of RS is generally highly unfavorable. However, the pattern of survival is not homogeneous and the clonal relationship between the CLL and the aggressive lymphoma clones is the most important prognostic factor. Rituximab-containing polychemotherapy represents the back-bone for induction treatment in RS. Younger patients who respond to induction therapy should be offered stem cell transplant to prolong survival."

**Condoluci, A. & Rossi, D.** 2017. Treatment of Richter's syndrome. *Curr Treat Options Oncol.* 2017 Nov 21;18(12):75. doi: 10.1007/s11864-017-0512-y.

"Based on the available literature, mostly derived from retrospective or non-randomized phase I or II studies, it is difficult to define an optimized treatment approach for patients developing Richter's syndrome (RS). Early recognition of chronic lymphocytic leukemia (CLL) patients presenting clinical features suspected for a transformation is useful to avoid exposing them to multiple lines of therapy that, being targeted to CLL progression, have poor efficacy against RS. Because of the low specificity (~ 50-60%) of clinical signs of RS (such as rapid and discordant bulky localized lymphadenopathies, elevated LDH levels, emergent physical deterioration, and/or fever in the absence of infection), a <sup>18</sup>F PET/CT and a biopsy are recommended to confirm RS. A <sup>18</sup>F PET/CT showing low uptake is helpful to rule out RS and avoid unnecessary risks and costs of performing a biopsy. A <sup>18</sup>F PET/CT showing a high uptake is not diagnostic of RS but may help in the choice of the site where the biopsy is to be performed. In the setting of the diffuse large B-cell lymphoma (DLBCL) variant of RS, the definition of a clonal relationship between RS and the underlying CLL may guide the choice of treatment. If a clonal relationship is confirmed (the most common situation), rituximab-CHOP-like treatment does not guarantee long-lasting remissions, and should be used as induction therapy followed by consolidation with a stem cell transplant in physically fit patients. If the CLL and RS are clonally unrelated (the less common situation), the management should be that of a de novo DLBCL. In the setting of the rare Hodgkin lymphoma variant of RS, which is usually clonally unrelated to the CLL, ABVD with or without radiotherapy may be curative of the aggressive lymphoma."



## About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The [South African National Clinical Trials Register](#) provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: [www.sanctr.gov.za/](http://www.sanctr.gov.za/)

**Appleby, N., Eyre, T.A., Cabes, M., Jackson, A., Boucher, R., Yates, R., Fox, S., Rawson, A., Hillmen, P. & Schuh, A. 2019.**

**Background:** Transformation of chronic lymphocytic leukaemia (CLL) to diffuse large B-cell lymphoma (DLCL) type Richter's syndrome (RS) carries a dismal prognosis. Standard-of-care chemoimmunotherapy for de novo RS is inadequate with median survival of less than one year. Patients are frequently elderly or have co-morbidities limiting dose-intense chemotherapy. Treatment of relapsed/refractory (R/R) RS and RS emerging after CLL-directed therapy represent urgent unmet clinical needs. Agents targeting Bruton's tyrosine kinase (BTK) deliver improved outcomes for patients with high-risk CLL and expand effective treatments to frailer patients. Acalabrutinib is an oral, second-generation BTK inhibitor with a favourable toxicity profile and demonstrated activity in CLL and B-cell lymphomas. Combination of acalabrutinib with standard-of-care CHOP-R chemoimmunotherapy offers a sound rationale to test in a prospective trial for de novo RS.

**Methods:** The prospective multicentre STELLAR study is designed in two elements, consisting of a randomised study to evaluate the safety and activity of CHOP-R chemoimmunotherapy in combination with acalabrutinib in newly diagnosed RS and single-arm studies of novel agents for other RS patient cohorts. Eligible patients with newly diagnosed DLBCL-type RS are randomised between six cycles of CHOP-R therapy and six cycles CHOP-R plus acalabrutinib, followed by acalabrutinib maintenance. The primary endpoint of the randomised component is progression free survival (PFS). Cohort 1 enrolls RS patients with progressive disease following chemoimmunotherapy for acalabrutinib monotherapy. Patients with RS diagnosed while on ibrutinib may enrol in Cohort 2, a single-arm study of CHOP-R plus acalabrutinib. The primary endpoint for the single-arm studies is overall response rate (ORR). Secondary endpoints for all cohorts are overall survival (OS), quality of life and proportion of patients proceeding to stem cell transplantation. The study will be accompanied by exploratory analysis of the mutational landscape of RS and the relationship between dynamic changes in sequential circulating tumour DNA samples and clinical outcomes.

**Discussion:** The STELLAR randomised trial evaluates the role of CHOP-R plus acalabrutinib in newly diagnosed RS patients. The single-arm platform studies enable the incorporation of promising novel therapies into the protocol. The STELLAR study has potential to identify novel biomarkers of treatment response in this high-risk malignancy.

**Trial registration:** EudraCT: 2017-004401-40, registered on the 31-Oct-2017. IRCTN: <https://www.irctn.com/IRCTN52839057>, registered on the 04-Mar-2019. ClinicalTrials.gov : [NCT03899337](https://clinicaltrials.gov/ct2/show/study/NCT03899337) , registered on 02-April-2019.

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The Cancer Association of South Africa (CANSA) has taken every precaution in preparing this Fact Sheet. Neither CANSA, nor any contributor(s) to this Fact Sheet shall be held responsible for any action (or the lack of any action) taken by any person or organisation wherever they shall be based, as a result, directly or indirectly, of information contained in, or accessed through, this Fact Sheet.



## Sources and References Consulted or Utilised

### About Health

<http://lymphoma.about.com/od/nonhodgkinlymphoma/qt/What-Is-Richters-Syndrome.htm>

**Appleby, N., Eyre, T.A., Cabes, M., Jackson, A., Boucher, R., Yates, R., Fox, S., Rawson, A., Hillmen, P. & Schuh, A.** 2019. The STELLAR Trial Protocol: a prospective multicentre trial for Richter's Syndrome consisting of a randomised trial investigation CHOP-R with or without Acalabrutinib for newly diagnosed RS and a Single-arm Platform Study for evaluation of novel agents in relapsed disease. *BMC Cancer*. 2019 May 20;19(1):471. doi: 10.1186/s12885-019-5717-y.

### Cancer Research UK

<http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/what-is-richters-syndrome>

**Condoluci, A. & Rossi, D.** 2017. Treatment of Richter's syndrome. *Curr Treat Options Oncol*. 2017 Nov 21;18(12):75. doi: 10.1007/s11864-017-0512-y.

**Eyre, T.A. & Schuh, A.** 2017. An update for Richter syndrome: new directions and developments. *Br J Haematol*. 2017 Aug;178(4):508-520. doi: 10.1111/bjh.14700. Epub 2017 Apr 25.

**Lenartova, A., Randen, U., Johannesen, T.B. & Teiønnfjord, G.E.** 2019. Richter Syndrome epidemiology in a large population based chronic lymphocytic leukemia cohort from Norway. *Cancer Epidemiol*. 2019 Jun;60:128-133. doi: 10.1016/j.canep.2019.04.002. Epub 2019 Apr 12.

### Leukaemia Foundation

<http://www.leukaemia.org.au/blood-cancers/leukaemias/chronic-lymphocytic-leukaemia-cll/richter-s-syndrome>

**Parikh, S.A., Kay, N.E. & Shanaftel, T.D.** 2014. How we treat Richter syndrome. *Blood*. 2014 Mar 13; 123(11): 1647–1657. Prepublished online 2014 Jan 13. PMID: PMC3954047.

### Richter's Syndrome

<https://www.youtube.com/watch?v=5FVmAVfkzEo>

**Roncati, L.** 2020. Richter's Syndrome of T-cell lineage (T Rex Lymphoma). *Curr Med Res Opin*. 2020 Mar;36(3):473-476. doi: 10.1080/03007995.2020.1713072. Epub 2020 Jan 13.

**Rossi, D.** 2016. Richter's syndrome: novel and promising therapeutic alternatives. *Best Pract Res Clin Haematol*. 2016 Mar;29(1):30-39. doi: 10.1016/j.beha.2016.08.006. Epub 2016 Aug 11.

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**Swords, R., Bruzzi, J. & Giles, F.** 2007. Recent advances in the diagnosis and therapy of Richter's syndrome. *Med Oncol.*, 24(1):17-32.

**Van Roosbroeck, K., Bayraktar, R., Calin, S., Bloehdorn, J., Dragomir, M.P., Okubo, K., Bertilaccio, M.T.S., Zupo, S., You, M.J., Gaidano, G., Rossi, D., Chen, S-S., Chiorazzi, N., Thompson, P.A., Ferraioli, A., Bertoni, F., Stilgenbauer, S., Keating, M.J. & Calin, G.E.** 2019. The involvement of microRNA in the pathogenesis of Richter Syndrome. *Haematologica*. 2019 May;104(5):1004-1015. doi: 10.3324/haematol.2018.203828. Epub 2018 Nov 8.

**Wikipedia**

[https://en.wikipedia.org/wiki/Non-Hodgkin\\_lymphoma](https://en.wikipedia.org/wiki/Non-Hodgkin_lymphoma)

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