
Chronic Neutrophilic Leukaemia (CNL)

**A Guide for
Patients**

Leukaemia Care
YOUR Blood Cancer Charity

Introduction

Being diagnosed with chronic neutrophilic leukaemia (CNL) can be a shock, particularly when you may never have heard of it. If you have questions about CNL – 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. For more personalised information, talk to your haematologist, clinical nurse specialist or hospital pharmacist.

This booklet was written by Isabelle Leach, Patient Information Writer at Leukaemia Care, and reviewed by Professor Mary Frances McMullin.

Disclaimer: *As we are accredited by the Information Standard, all of our information has to adhere to a standardised process that ensures it is of the highest quality. Unfortunately, due to the rarity of CNL, we were unable to complete the production process which meant*

that this booklet cannot be formally accredited. However, we assure you that this information was created with the same values as that which is.

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 9.00am - 10.00pm on weekdays and 9.00am - 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@leukaemicare.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.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@leukaemicare.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.leukaemicare.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@leukaemicare.org.uk**

Patient magazine

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

What is CNL?

Neutrophils are a type of white blood cell that form part of the body's immune system. These have a protective immunity role against bacterial infections and inflammation. The normal count for neutrophils in peripheral blood is less than $7.7 \times 10^9/l$ with a normal total white blood cell count of less than $11 \times 10^9/l$. Neutrophils are the most common white blood cells accounting for 40% to 80% of all white blood cells. While the most common causes for neutrophilia (increase in number of neutrophils) is infection and inflammation, neutrophilia may also be the result of cancer.

Chronic neutrophilic leukaemia (CNL) is an extremely rare cancer originating in the bone marrow. To date, approximately only 200 patients have been identified. The median age of the patients was 65 years at diagnosis, and 67% were male.

CNL is characterised by the following:

- Continued production of mature neutrophils (which is

not being caused by anything else)

- Bone marrow white blood cell hyperplasia (enlargement of an organ/tissue due to an increase in the rate of reproduction of its cells)
- Hepatosplenomegaly (enlarged liver and spleen)

For details of the conditions required to make the diagnosis of CNL, see the section **How is CNL diagnosed?**

Prognosis

CNL may stay the same for many years or it may progress quickly to acute leukaemia. So far, cases have only transformed into acute myeloid leukaemia (AML). Patients' risk factors, which will determine their likely outcome are evaluated individually by your doctor.

Median survival calculated from a number of CNL case reports is between 21 to 30 months, however, the small number of people diagnosed with CNL does not allow for an accurate

estimate. Some people may survive much longer after diagnosis, with case reports of CNL patient's survival ranging from six months to more than 20 years, with a five-year survival of 28%.

A recent series of 16 case reports of patients with CNL, all of whom had the CSF3RT618I mutation, showed a median overall survival of 24 months, which is similar to previous reports above.

If you would like more information about acute myeloid leukaemia (AML) you can order a booklet by calling the Patient Services team on **08088 010 444**.

What are the symptoms of CNL?

Patients with CNL do not normally present with specific symptoms apart from maybe fatigue or easy bruising. Often a routine blood test or medical exam will show an abnormal blood cell count or enlarged liver and/or spleen.

In due course, the excess of neutrophils circulating in the peripheral blood will cause symptoms such as:

- Fatigue
- Weight loss
- Easy bruising
- Bone pain
- Night sweats
- Enlarged spleen (causing a feeling of fullness below the ribs on the left side)
- Enlarged liver

At Leukaemia Care we have a freephone helpline service available for patients and carers who are affected by a blood cancer. We can provide emotional and practical support as well as medical advice. The telephone number of the helpline is **08088 010 444**.

How is CNL diagnosed?

According to the 2008 WHO classification system for tumours of the haematopoietic and lymphoid tissues, the diagnostic criteria for CNL were:

- White cell count greater than $25 \times 10^9/l$
- More than 80% of mature neutrophils
- Less than 10% of immature neutrophils
- Absence of the following conditions:
 1. Granulocytic dysplasia (abnormal growth of white blood cells called granulocytes)
 2. Myelodysplasia in other cells in the bone marrow other than granulocytes
 3. Monocytosis (increased levels of monocytes which are white blood cells that become scavenger cells to clear infection in the immune

system)

4. Eosinophilia (increased levels of eosinophils which are white blood cells that have a protective immunity role against parasites and allergens)
5. Basophilia (increased levels of basophils which are white blood cells that are responsible for inflammatory reactions during an immune response)

In 2013, the discovery of the T618I mutation of CSF3R gene (colony-stimulating factor 3 receptor) in over 80% of CNL patients has greatly clarified the field of research in CNL. This CSF3RT618I mutation represents a biomarker for diagnosis. The new edition of the 2016 World Health Organization (WHO) classification system for tumours of the hematopoietic and lymphoid tissues, now includes the CSF3RT618I mutation in its diagnostic

How is CNL diagnosed? (cont.)

criteria for CNL.

While CSF3RT618I mutations occur in more than 80% of patients with CNL, they do not occur in some 20% of CNL patients, and these mutations are also known to occur in patients with atypical CML. Consequently, the WHO diagnosis 2016 also requires the exclusion of other causes of neutrophilia, including infections and inflammatory processes, metastatic cancer, and plasma cell cancers with secondary neutrophilia. Demonstration of the absence of the BCR-ABL1 mutation, PDGFRA, PDGFRB, or FGFR1, or PCM1-JAK2 rearrangements helps exclude atypical chronic myeloid leukaemia (CML) and chronic eosinophilic leukaemia.

Other mutations:

Several recent studies have found other mutations in CNL patients, including JAK2 (Janus Kinase 2), CALR (Calreticulin),

ASXL1 (Additional sex combs-like 1) and SETBP1 (SET binding protein 1) mutations. Further research is needed to determine whether these mutations can serve as prognostic markers that will help guide doctors making treatment decisions.

WHO diagnostic criteria for CNL

1. Peripheral blood white blood cells greater or equal to $25 \times 10^9/l$
 - Segmented/immature neutrophils greater or equal to 80% of white blood cells
 - Neutrophil precursors less than 10% of white blood cells
 - Myeloblasts rarely observed
 - Monocyte count less than $1 \times 10^9/l$
 - No dysgranulopoiesis
2. Hypercellular bone marrow
 - Neutrophil granulocytes

increased in percentage and number

- Neutrophil maturation appears normal
- Myeloblasts = 5% of nucleated cells

3. Not meeting WHO criteria for

- Chronic myeloid leukaemia - BCR-ABL1
- Polycythaemia vera (proliferation of red blood cells)
- Essential thrombocythaemia (excess production of platelets leading to abnormal blood clotting)
- Primary myelofibrosis (build-up of scar tissue in the bone marrow)

4. No rearrangement of PDGFRA, PDGFRB, or FGFR1, or PCM1-JAK2 to exclude

- Chronic neutrophilic leukaemia (excess production of white cells called neutrophils)

- Atypical CML

5. Presence of CSF3R T618I or other activating CSF3R mutation

OR

In the absence of a CSF3R mutation,

- Persistent neutrophilia of at least three months
- Splenomegaly and no identifiable cause of reactive neutrophilia including absence of a plasma cell cancer
- Or, if present, demonstration of clonality of myeloid cells by chromosomal or molecular studies

Diagnostic Tests

The diagnosis of CNL requires a number of investigations to be able to apply the 2016 WHO diagnostic criteria for CNL.

- Blood samples to measure the complete blood cell counts (number and quality of white

How is CNL diagnosed? (cont.)

blood cells, red blood cells and platelets)

- Bone marrow biopsies: samples of bone marrow cells are obtained by bone marrow aspiration.

The cells from the blood and marrow samples are examined under a microscope by a haematologist (doctor who specialises in diseases of the blood). To achieve a definite diagnosis, the bone marrow will be examined for the following:

- Cell genetic abnormalities
- Karyotyping: This evaluates the number and structure of the chromosomes to identify any abnormalities.
- Polymerase chain reaction test: This test is occasionally performed to determine certain changes in the structure or function of genes.

Risk of transformation in CNL

Transformation to AML is reported to occur in 10% to 20% of patients. The median time of an AML transformation is 21 months with a range of three to 94 months.

How is CNL treated?

Prior to the discovery of the CSF3RT618I gene, there were no specific treatments for CNL because of the rarity of the disease and the consequent lack of clinical trials. Management choices from other types of chronic leukaemia have been tried, but without achieving any improvements.

Therapy options were therefore initially targeted at managing the symptoms. Splenic irradiation (use of high-energy radiation from X-rays, gamma rays, or neutrons to kill cancer cells and shrink tumours) and a splenectomy (removal of the spleen) were used to decrease abdominal pain caused by the enlarged spleen. A splenectomy, however, caused an increase in neutrophils and is only really used as a palliative measure.

Other treatments included cytoreductive drugs (drugs to decrease the size of the tumour) such as oral hydroxycarbamide (also known as hydroxyurea), and interferon-alpha (IFN-a)

to control the growth of cancer cells. IFN-a is a known immunotherapy, which consists of purified derivative from fractions of white blood cells from the blood. Immunotherapy acts by boosting the body's natural immune system to fight the leukaemia.

Drugs that have been used in the treatment of patients include interferon, thalidomide, cladribine, imatinib and ruxolitinib.

Interferon

IFN-a is the only treatment which has been shown to give durable remissions in CNL as shown in a number of reports.

A review of 14 cases of patients with CNL featured a patient who achieved clinical remission for 41 months while being treated with IFN-a. However, in another case report, one patient with CNL achieved a partial response for at least two years when they received IFN-a in combination with hydroxycarbamide, but then

How is CNL treated? (cont.)

suffered progression of his CNL.

Chemotherapy

Chemotherapy is the use of drugs to prevent the ability of cancer cells to grow and divide, thereby destroying the cancer cells over time. Targeted therapy is a treatment that targets the specific genes or proteins of leukaemia cells, as is the case for ruxolitinib.

Ruxolitinib

Ruxolitinib is a JAK inhibitor which is currently indicated for the treatment of patients with polycythaemia vera and myelofibrosis (serious cancer characterised by bone marrow fibrosis). It has shown promise for CNL and atypical CML.

CSF3R mutations have been shown to disrupt JAK/STAT (signal transducer and activator of transcription) signalling. The JAK-STAT signalling pathway is a chain of interactions between proteins in a cell, and is involved in processes such as immunity and cancer. Therefore, it has been suggested that JAK inhibitors,

such as ruxolitinib, may be effective in treating patients with CNL who have CSF3R mutations.

Maxson et al, who first described the CSF3R T618I mutation, reported that one of their patients who had the CSF3R T618I mutation was treated with ruxolitinib 10mg orally twice daily. The patient showed a significant decrease in the number of neutrophils and white blood cells, as well as normal platelet (tiny blood cells that help clot blood) levels. When the dose was increased to 15mg twice daily, the patient showed improvement after 11 months of treatment.

In another case of CNL, where the patient had the CSF3R mutation (T618I/G739), treatment with ruxolitinib for 11 months decreased the white cell count from 50% to 8%. This was maintained for a further nine months, before the patient relapsed.

Conversely, less convincing responses have also been experienced with ruxolitinib

in patients with CNL. Three case reports of patients with CNL associated with CSF3R and SETBP1 mutations showed variable outcomes following treatment with ruxolitinib.

- In one of the case reports, a patient with both CSF3RT618I and SETBP1 mutations, did not show any meaningful improvement with hydroxycarbamide, so ruxolitinib 10mg orally daily was added to the patient's treatment. The patient stopped responding to both treatments, and acquired a higher white blood cell count when the doses were increased to ruxolitinib 20mg twice daily and hydroxycarbamide 1g orally daily.
- In the two other case reports of CNL, both patients had CSF3RT618I and SETBP1G870S mutations and received ruxolitinib 20mg orally daily. They showed responses of five and nine months. In the case reported by Stahl et al, the patient improved after only two weeks of treatment, whereas in

the case reported by Nooruddin et al 2017, the patient who also had an ASXL1 mutation, had a worse outcome which is thought to be due to interference from the ASXL1 mutation.

Despite CSF3R mutations being present in a large number of patients with CNL, they are not the only gene mutations implicated in CNL. The other mutations, such as the SETBP1 or ASXL1 mutations, are thought to be interacting with the CSF3R mutation to explain this differing efficacy.

To further clarify the role of ruxolitinib in CNL patients with varying mutations, a multicentre phase 2 clinical trial (NCT02092324) is currently in progress to determine the proportion of patients with CNL and aCML who respond to ruxolitinib. The study started on 5 May 2014 and is due to be completed in April 2019.

Induction chemotherapy

Standard induction therapy with

How is CNL treated? (cont.)

anthracycline and cytarabine in the accelerated or blast phases of CNL has failed to achieve lasting remission.

Other therapies have included drugs such as hypomethylating agents (four patients), thalidomide (two patients), cladribine (two patients) and imatinib (one patient). However, none of these treatments have enabled patients to achieve remission.

Stem cell transplant

Because of the possibility of progression to blast transformation and the number of cases that become refractory, allogeneic stem cell transplantation (ASCT) has been used for a number of patients. An ASCT is the receipt of blood forming stem cells from a genetically similar, but not identical, donor. At present, ASCT is the only known curative option for patients.

In view of the rarity of CNL, only data from case reports of ASCTs are available. A case report series of nine patients aged from 15

to 60 years, who received ASCT from sibling donors or matched unrelated donors, showed successful ASCTs for six patients (66.7%) with periods of ongoing remission varying from one to 78 months.

- All but one of these patients received myeloablative conditioning, which involves giving the patient chemotherapy or irradiation just before the transplant to eradicate the patient's cancerous cells before infusing the donor blood forming stem cells, and also to suppress immune reactions.
- Of the three patients whose ASCT was not successful, two of the patients received transplants following blast transformation and in the accelerated phase. Both died shortly after the transplant due to toxicity and/or relapse.

Results from other series have confirmed that patients receiving ASCT in the blast or accelerated phases appear to experience worse outcomes with

regards to toxicity and/or early relapse.

Despite no firm evidence, it appears that ASCT is best performed in the chronic phase of CNL. Therefore, it may be prudent to have patients evaluated for ASCT early in their disease and certainly before the blast transformation stage.

Supportive care

Supportive or palliative care is medical care that relieves symptoms without dealing with the cause of the condition.

Hydroxycarbamide has previously been the most used treatment in patients with CNL as it reduces the white blood cell count and the splenomegaly, which is caused by the greatly increased numbers of white blood cells.

After initial efficacy with hydroxycarbamide, most patients in a CNL case series no longer respond to their treatment (it becomes refractory). In addition, nearly 25% of these patients were refractory to hydroxycarbamide from the start of treatment.

A splenectomy, which is an operation to remove the

spleen may be recommended for some patients to relieve symptoms of abdominal pain. A surgical oncologist who is a doctor specialising in cancer surgery will usually perform this procedure.

When making treatment plan decisions, patients are often encouraged to consider clinical trials as an option; they may give access to new treatments being investigated. Your physician can guide you in this decision. Any clinical trials that are recruiting can be found at: <https://clinicaltrials.gov/>

Follow-up

Follow-up after treatment is an important part of cancer care. Follow-up for chronic neutrophilic leukaemia is often shared among the haematologists and your family doctor. Your healthcare team will work with you to decide on follow-up care to meet your needs.

Glossary

Acute Leukaemia

Leukaemia is a cancer of the white blood cells. Acute leukaemia means it progresses rapidly and aggressively, and usually requires immediate treatment.

Acute Myeloid Leukaemia

Acute myeloid leukaemia (AML) is a type of blood cancer that starts from young blood cells called granulocytes or monocytes in the bone marrow.

Chemotherapy

A type of cancer treatment that uses one or more drugs with a powerful chemical to kill growing cancer cells.

Chronic Leukaemia

A type of blood cancer that affects the white blood cells. This tends to progress over many years.

Chronic Myeloid Leukaemia

A cancer that affects the blood and bone marrow defined by the presence of BCR-Abl translocation.

Clinical trial

A highly regulated research study which assigns patients and non-patients to participate in the study and to evaluate the efficacy of a drug or a combination of drugs.

Fatigue

Extreme tiredness, which is not alleviated by sleep or rest. Fatigue can be acute and come on suddenly or chronic and persist.

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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