

Highlights

- Chronic neutrophilic leukemia (CNL) is one of a group of related blood cancers known as “myeloproliferative neoplasms” (MPNs) in which marrow cells that produce blood cells develop and function abnormally.
- CNL is an extremely rare disease. To date, the World Health Organization (WHO) has only reported approximately 200 patients who have been diagnosed with CNL.
- In CNL, neutrophils (a type of white blood cell) are overproduced and accumulate in the peripheral blood and the bone marrow. Signs, symptoms and complications of CNL result from the overproduction of neutrophils.
- There is no standard treatment for CNL. The disease has primarily been treated with hydroxyurea and other oral chemotherapy agents, as well as interferon-alpha. Allogeneic stem cell transplantation is a potentially curative option for eligible patients.
- The recent discovery of the CNL-defining mutation of *CSF3R* as well as other advances in the understanding of the molecular basis of the disease, is expected to guide the development of new and more effective therapies.
- Ruxolitinib, a JAK1/JAK2 kinase inhibitor drug that is FDA approved to treat myelofibrosis and polycythemia vera, is currently being studied in a clinical trial for the treatment of CNL.

Introduction

According to the World Health Organization (WHO), chronic neutrophilic leukemia (CNL) belongs to a group of blood cancers known as “myeloproliferative neoplasms” (MPNs). MPNs share several features, notably the clonal production of blood cells. All clonal diseases are types of cancer that begin with one or more changes (mutations) to the DNA of a single cell. In CNL, the result is that the bone marrow produces an excess number of neutrophils. A neutrophil is a white blood cell that is involved in the body’s immune response against viruses, bacteria and fungus.

Other MPNs include polycythemia vera, essential thrombocythemia and myelofibrosis. Over the past five years there have been major advances in the understanding of the molecular abnormalities associated with MPNs, and CNL in particular. It is hoped that this knowledge can be used to direct and develop new and more effective therapies that will improve outcomes for CNL patients.

This fact sheet provides patients who have CNL with additional information about diagnosis, treatment, clinical trials, expected outcomes and available support resources.

Chronic Neutrophilic Leukemia (CNL)

Chronic neutrophilic leukemia (CNL) is a clonal disorder, in which a group of identical cells are multiplying uncontrollably. These cells originate from a DNA mutation within a single cell. In CNL, these changes affect the normal growth and development of a type of white blood cell called a “neutrophil.”

Neutrophils travel to the site of an infection. They fight the infection by ingesting microorganisms and releasing enzymes that kill the microorganisms. Neutrophils make up about 40 to 80 percent of the cells in normal human blood.

CNL is characterized by sustained neutrophilia (an excess number of neutrophils) circulating in the peripheral blood, which leads to the symptoms and the complications of the disease.

The course of CNL varies. The disease can either develop slowly or it can progress rapidly. Within two years of initial

diagnosis, CNL tends to progress to a more aggressive type of leukemia, usually acute myeloid leukemia (AML). Currently, there is no standard therapy for CNL and treatment options are geared towards managing rather than curing the disease. However, hopefully, recent developments in the understanding of the genetic and molecular features of CNL will have an impact on prognosis and patient outcomes.

CNL Incidence

CNL, an extremely rare disease, was first described in the medical literature in 1920. In 2001, CNL finally attained formal recognition as a distinct disease and was included in the World Health Organization (WHO) classification system. Since then, WHO has reported that only about 200 patients have been diagnosed with CNL. The median age at diagnosis is 66 years but the disease has affected persons of all ages, ranging from 15 to 86 years. CNL affects both women and men equally.

Signs and Symptoms of CNL

Most patients have no symptoms at diagnosis and during the early stages of the disease. However, as neutrophil counts increase and the disease progresses, people may experience

- 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.

Diagnosis of CNL

Patients with CNL do not present with specific symptoms. They may have visited their doctor complaining of fatigue or easy bruising. If a routine medical exam reveals an enlarged liver and/or spleen, as well as an abnormal blood count, CNL or some other myeloproliferative neoplasm may be suspected.

A CNL diagnosis is made based on the WHO criteria (see Table 1 on page 3). Usually, a definitive diagnosis cannot be confirmed just because there were abnormal blood counts or findings from a single lab test. A patient will be monitored

and repeated lab tests will be performed in order to rule out other types of MPN.

Blood and Bone Marrow Tests. Blood samples are generally taken from a vein in the patient's arm. Samples of marrow cells are obtained by bone marrow aspiration and biopsy. The cells from the blood and marrow samples are examined by a hematopathologist under a microscope. Any change in the number and appearance of blood cells is noted and described and will help the patient's doctor to make an accurate diagnosis.

Besides an abnormally high neutrophil count (one of the key characteristics of CNL), other findings from blood tests may include

- **Mild anemia (low levels of red blood cells)**—Hemoglobin level about 11g/dl
- **Platelet count that is normal or slightly decreased**—The platelet count tends to decrease in later stages of CNL and with increasing enlargement of the liver and spleen
- **Elevated LDH (lactate dehydrogenase) level**—LDH is an enzyme found in all normal and abnormal cells. It is released from cells into the blood and is associated with energy production. An increased LDH level in the blood may be a sign of tissue damage, some types of cancer or other diseases.
- **Elevated vitamin B₁₂ levels**
- **Elevated leukocyte alkaline phosphatase (LAP) levels**—LAP is an enzyme found in white blood cells. An elevated level may be present in people with chronic inflammation, certain types of cancer or other medical conditions.

Other Tests. Karyotyping and cytogenetic analysis are laboratory tests used to identify certain changes in chromosomes and genes. A test called a “polymerase chain reaction” (PCR) may be done. In this test, cells in blood or marrow samples are studied to look for certain changes in the structure or function of genes.

Table 1. World Health Organization (WHO) Criteria for CNL Diagnosis

CNL Diagnostic Criteria
<p>1. Peripheral blood leukocytosis</p> <ul style="list-style-type: none"> Increased number of white blood cells circulating in the peripheral blood $\geq 25 \times 10^9/L$
<p>2. Bone marrow biopsy that shows a greater than normal percentage of bone marrow cells</p> <ul style="list-style-type: none"> Neutrophils increased in percentage and number Neutrophil maturation appears normal Myeloblasts (immature cells) <5%
<p>3. Does not meet WHO criteria for CML <i>BCR-ABL 1+</i>, PV, ET or PMF</p>
<p>4. No genetic rearrangement (mutation) of</p> <ul style="list-style-type: none"> <i>PDGFRA</i> – platelet-derived growth factor receptor, alpha polypeptide [as seen in chronic eosinophilic leukemia (CEL)] <i>PDGFRB</i> – platelet-derived growth factor receptor, beta polypeptide [as seen in chronic myelomonocytic leukemia (CMML)] <i>FGRF1</i> – fibroblast growth factor receptor 1 [as seen in chronic eosinophilic leukemia (CEL) and some subtypes of acute myeloid leukemia (AML)] <i>PCMI-JAK2</i> – [as seen in atypical chronic myeloid leukemia (aCML) and erythroid leukemia]
<p>5. Presence of <i>CSF3R T618I</i> or other activating <i>CSF3R</i> mutation OR In the absence of a <i>CSF3R</i> mutation</p> <ul style="list-style-type: none"> Persistent neutrophilia (at least 3 months) Enlarged spleen (splenomegaly) No identifiable cause of reactive neutrophilia including absence of a plasma cell neoplasm If reactive neutrophilia is present, demonstration of malignant myeloid cells by cytogenetic or molecular studies

PV = polycythemia vera PMF = primary myelofibrosis
 ET = essential thrombocythemia CML = chronic myeloid leukemia
PCMI-JAK2 = pericentriolar material 1-Janus kinase 2
CSF3R = colony-stimulating factor 3 receptor

Chromosomal and Gene Mutations. Most CNL patients have no chromosomal abnormalities at diagnosis. The most common abnormalities reported in a few case studies included trisomy 8, trisomy 21, del (20q) and del (11q).

CSF3R mutation. Over the past few years, great progress was made in understanding the molecular basis of CNL with the discovery of a disease-defining mutation in *CSF3R*, the receptor for colony-stimulating factor 3. Colony-stimulating factor 3 is the primary growth factor of neutrophil production.

Recent studies indicate that most CNL patients (up to 90 percent of them) carry the *CSF3R* mutation. The *CSF3R* mutation falls into two categories: truncation mutations and membrane proximal mutations. *CSF3R* membrane proximal mutations may exhibit drug sensitivity to JAK kinase inhibitors such as ruxolitinib (Jakafi®).

These new findings are expected to result in better outcomes for CNL patients, because the *CSF3R* mutation is becoming a biomarker for diagnosing the disease and will also provide a target for therapy.

Other mutations. A small number of studies have found other mutations in some CNL patients, including *JAK2* (Janus kinase 2), *CALR* (calreticulin), *ASXL1* and *SETBP1* (SET binding protein 1) mutations. Further investigation is needed to determine whether these mutations can serve as prognostic markers that will help guide doctors making treatment decisions.

Treatment of CNL

Because of its very low incidence, there is no standard of care for CNL. The treatment of CNL has focused on managing symptoms and complications rather than curing the disease. Unfortunately, once the disease progresses to acute myeloid leukemia, there is probably only a slight chance of obtaining a long-lasting remission.

Allogeneic stem cell transplantation is the only potentially curative option for CNL patients, providing that they are able to undergo this procedure.

Patients are advised to discuss their situation with their doctor to determine the most appropriate treatment. It is important to seek treatment from a hematologist-oncologist who is experienced in treating a myeloproliferative neoplasm such as CNL or perhaps from a hematologist-oncologist who is in consultation with a CNL expert at a cancer center.

Drug Therapy for CNL. CNL has primarily been treated with hydroxyurea and other oral chemotherapy agents, as well as interferon-alpha.

Hydroxyurea is the drug that is most commonly used to treat CNL. It is effective in controlling elevated white blood cell counts and spleen enlargement until there is evidence of disease progression or blast transformation. In some cases, when CNL has become either resistant or refractory to hydroxyurea, other agents including cladribine, thalidomide and ruxolitinib have been used but only temporary responses have been achieved.

Interferon-alpha has shown success in a few cases where it has induced durable responses. In some instances, it has been used intermittently for treating progressive disease.

To date, there have been no instances of hematologic complete remission for either accelerated- or blast-phase CNL following standard induction chemotherapy (using anthracyclines and cytarabine).

Stem Cell Transplantation (SCT) for CNL. Due to the potential for progressive refractory neutrophilia and transformation to acute myeloid leukemia, allogeneic SCT represents the only curative option for CNL. Allogeneic SCT has been used in a limited number of cases to treat, and sometimes cure, CNL patients.

There are a few reports of successful allogeneic SCT in eligible patients who have experienced long-lasting remissions (ranging from a few months to several years). At this time, there is no information available on the use of other forms of transplantation such as nonmyeloablative, cord-blood or autologous transplantation for CNL.

Patients are advised to discuss whether SCT is a good treatment option for them with their doctor.

Treatments Under Investigation

Clinical trials test new drugs and treatments, many of which are supported by LLS research programs, before they are approved by the Food and Drug Administration (FDA) as standard treatments. Clinical trials are carefully controlled research studies, conducted under rigorous guidelines, to help researchers determine the beneficial effects and possible adverse side effects of new treatments.

Patient participation in clinical trials is important in the development of new and more effective treatments and may provide patients with additional treatment options. Patients interested in participating in clinical trials are encouraged to talk to their doctors about whether a clinical trial would be appropriate for them.

Ruxolitinib (Jakafi®) is a JAK1/JAK2 kinase inhibitor, currently FDA approved to treat patients with intermediate- or high-risk myelofibrosis and polycythemia vera who are intolerant or nonresponsive to hydroxyurea treatment. Although this drug is not yet approved for CNL, there are several reports of patients with *CSF3R* mutated CNL who have been treated with ruxolitinib and who have had positive outcomes. This drug is currently being studied in clinical trials for the treatment of CNL and atypical CML.

For more information about clinical trials, call an LLS Information Specialist at (800) 955-4572, see the free LLS booklet *Understanding Clinical Trials for Blood Cancers* at www.LLS.org/booklets or visit www.LLS.org/clinicaltrials.

Outcomes for CNL Patients

The likely outcome of a disease, called the “prognosis,” varies in patients with CNL. Each patient’s risk factors, which affect his or her prognosis, are evaluated individually. For CNL, the reported median survival either approaches or exceeds 23.5 months. Some people may survive much longer after diagnosis. Some studies have indicated that CNL patient survival is variable, ranging from 6 months to more than 20 years.

In general, statistics may underestimate survival rates to a small degree since they may not reflect the most recent advances in treatment.

All patients are advised to discuss survival information with their doctors. Keep in mind that outcome data can only show how other people with CNL responded to treatment, but cannot predict how any one person will respond.

The recent advances in the understanding of CNL are expected to have a significant impact on the clinical management of the disease as well as improve outcomes for patients.

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the United States and in Canada. To find the chapter nearest to you, visit our Web site at www.LLS.org/chapterfind or contact

The Leukemia & Lymphoma Society

3 International Drive, Suite 200
Rye Brook, NY 10573

Contact an Information Specialist at (800) 955-4572
Email: infocenter@LLS.org.

LLS offers free information and services for patients and families touched by blood cancers. The following entries list various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/information specialists
- Visit: www.LLS.org/information specialists.

Free Information Booklets. LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered. For more information, please visit www.LLS.org/booklets.

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/espanol.

Telephone/Web Education Programs. LLS offers free telephone/Web education programs for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

LLS Community. Community is an online social network and registry for patients, caregivers, and supporters of those with blood cancer. It is a place to ask questions, get informed, share your experience, and connect with others. To join visit www.LLS.org/community.

Online Blood Cancer Discussion Boards and Chats. Online discussion boards and moderated online chats can help cancer patients reach out, share information and provide support. For more information, please visit www.LLS.org/discussionboard and www.LLS.org/chat.

Sign Up for an E-Newsletter. Read the latest disease-specific news, learn about research studies and clinical trials, and find support for living with blood cancer. Please visit www.LLS.org/signup.

LLS Chapters. LLS offers support and services in the United States and Canada including *The Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your chapter, please

- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind.

Clinical Trials (Research Studies). New treatments for patients are ongoing. Patients can learn about clinical trials and how to access them. For more information, please call (800) 955-4572 to speak with our LLS Information Specialist who can help conduct clinical-trial searches.

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy.

Other Resources

The Myeloproliferative Disorders Research Consortium (MPD-RC)

www.mpdrc.org

The MPD-RC is an international, multi-institutional nonprofit consortium funded by the National Cancer Institute. It is set up to coordinate, facilitate and perform basic and clinical research on Philadelphia chromosome-negative myeloproliferative neoplasms (Ph-MPNs).

National Cancer Institute (NCI)

www.cancer.gov
(800) 422-6237

The National Cancer Institute (NCI), part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including CNL. The NCI also provides a clinical-trial search feature, the PDQ® Cancer Clinical Trial Registry, at www.cancer.gov/clinicaltrials, where CNL patients can look for clinical trials.

The National Organization for Rare Disorders (NORD)

www.rarediseases.org
(800) 999-6673/(203) 744-0100

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare “orphan” diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research and service.

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