LEUKEMIA & LYMPHOMA SOCIETY®

Chronic Neutrophilic Leukemia

No. 30 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- Chronic neutrophilic leukemia (CNL) is one of a group of related blood cancers known as "myeloproliferative neoplasms" (MPNs). In these cancers, the bone marrow cells that produce different types of blood cells don't develop the way they should.
- CNL is a very rare disease. To date, the World Health Organization (WHO) has reported just over 200 patients with CNL.
- CNL is determined by the presence of a mutation in the *CSF3R* gene. This mutation is found in most people with this disease.
- In CNL, the body makes too many neutrophils, a type of white blood cell. They build up in the blood and the bone marrow. Signs, symptoms and complications of CNL are caused by having too many neutrophils.
- There is no standard treatment for CNL. It's most often treated with hydroxyurea and other oral chemotherapy drugs. Interferon-alpha might also be used. Most recently, targeted therapy has been found to help treat CNL. Allogeneic stem cell transplantation may be a curative option for some patients.
- The discovery of the *CSF3R* gene mutation, as well as other advances in understanding the genetics of CNL, is expected to lead to better treatments in the future.

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 are cancers that cause the bone marrow to make too many of one kind of blood cell. Normally, marrow cells develop into 3 types of blood cells: red blood cells, white blood cells, or platelets. Neutrophils are one type of white blood cells. A neutrophil, like other white cells, helps fight viral, bacterial, and fungal infections. In chronic neutrophilic leukemia (CNL), the bone marrow makes too many neutrophils.

MPNs start because of one or more genetic changes (mutations) in the DNA of a single bone marrow cell. Other MPNs include chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (PMF).

Over the past five years there have been major advances in understanding the molecular and genetic changes linked to CNL. It's hoped that this knowledge can be used to develop new and better treatments that will improve outcomes for CNL patients.

This fact sheet can help people who have CNL learn more about its diagnosis, treatment, clinical trials, expected outcomes and available resources.

Chronic Neutrophilic Leukemia (CNL)

Chronic neutrophilic leukemia (CNL) is a "clonal" disorder. This means a group of identical cells are growing and dividing out of control. This process starts with a DNA change or mutation in a single cell. The mutation causes the cells to reproduce when they should not. In CNL, this starts in one neutrophil cell.

Neutrophils are part of the immune system. They're one of the first blood cells to travel through the blood to the site of an infection. They fight infection by ingesting or engulfing micro-organisms, then releasing enzymes that kill these micro-organisms. Neutrophils make up about 40% to 80% of the total cells in normal human blood. Neutrophils live for only a few hours, so the bone marrow is constantly making new neutrophils.

CNL is caused by an excess number of neutrophils (a condition called "neutrophilia"). They build up in the blood, which can, over time, cause abnormal blood cell levels that can lead to symptoms including bleeding problems, infections and organ damage.

The course of CNL varies. It can develop slowly or it can progress rapidly. Within two years of diagnosis, CNL tends to progress to a fast-growing type of leukemia, usually acute myeloid leukemia (AML).

There's no standard treatment for CNL. Current treatment is used to manage rather than cure the disease. It's hoped that ongoing progress in the understanding of the genetic and molecular features of CNL will have an impact on treatment and patient outcomes.

CNL Incidence

CNL is a very rare disease. It was first described in the medical literature in 1920. In 2001, CNL was recognized as a distinct disease and was included in the World Health Organization (WHO) classification system. Since then, WHO has reported that just over 200 patients have been diagnosed with CNL. It has been diagnosed in people ranging from age 15 to 86 years but is most common in people over age 50. CNL is slightly more common in males than in females.

Signs and Symptoms of CNL

Most people have no CNL symptoms when they're diagnosed or during the early stages of the disease. But as the number of neutrophils in the blood increases, people may experience:

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

Diagnosis of CNL

People with CNL seldom have specific symptoms. Fatigue or easy bruising may have led them to see a doctor, where a test may reveal abnormal blood counts. Sometimes a routine physical exam reveals an enlarged spleen and/or liver. In cases like these, CNL or some other myeloproliferative neoplasm (MPN) may be suspected.

CNL is diagnosed based on World Health Organization (WHO) criteria (see **Table 1**). In most cases, one test showing abnormal blood counts is not enough to diagnose CNL. A patient will be monitored, and lab tests will be repeated in order to rule out other problems. It's also important to rule out other types of MPN. For instance, CNL cells will **not** have the Philadelphia chromosome or the *BCR-ABL1* fusion gene, changes that are commonly found in chronic myeloid leukemia (CML).

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

CNL Diagnostic Criteria
1. Peripheral blood leukocytosis • Increased number of white blood cells circulating in the peripheral blood ≥25 x 10^9/L • Mature and immature neutrophils form ≥80% of WBCs • Myeloblasts are rarely observed • Monocyte count <1 x 10^9/L • No dysgranulopoiesis (granulocytes do not form or develop properly)
2. Bone marrow biopsy that shows a greater than normal percentage of bone marrow cells • Neutrophils increased in percentage and number • Neutrophil maturation appears normal • Myeloblasts (immature cells) <5%
3. Does not meet WHO criteria for CML MPNs *BCR-ABL 1+*, polycythemia vera (PV), essential thrombocytosis (ET) or primary myelofibrosis (PMF)
4. No genetic rearrangement (mutation) of: • *PDGFRA* – platelet-derived growth factor receptor alpha polypeptide; as seen in chronic eosinophilic leukemia (CEL) • *PDGFRB* – platelet-derived growth factor receptor beta polypeptide; as seen in chronic myelomonocytic leukemia (CMML) • *FGRF1* – fibroblast growth factor receptor 1; as seen in chronic eosinophilic leukemia (CEL) and some subtypes of acute myeloid leukemia (AML) • *PCM1-JAK2* – as seen in atypical chronic myeloid leukemia (aCML) and erythroid leukemia
5. Presence of *CSF3R T618I* or other activating *CSF3R* mutation **OR** **Absence of a *CSF3R* mutation** • 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

CML, chronic myeloid leukemia; *PCM1-JAK2*, pericentriolar material 1-Janus kinase 2; *CSF3R*, colony-stimulating factor 3 receptor; WBC, white blood count.

Blood and Bone Marrow Tests. Blood and bone marrow tests are used to diagnose CNL. Blood is usually taken from a vein in the patient's arm. For a bone marrow aspiration and biopsy, tiny pieces of bone and bone marrow are removed from the patient, usually taken from the back of the hip. The blood and bone marrow samples are sent to a lab for testing. A hematopathologist looks at the cells under a microscope. This doctor has special training in examining and testing cells to diagnose diseases. Tests are done to measure the numbers of cells and to find changes in the way the cells appear.

In addition to an abnormally high neutrophil count (one of the key changes caused by CNL), other blood test findings may include:

- **Mild anemia (low levels of red blood cells)** — Hemoglobin level at about 11g/dL
- **Decreased platelet count** — The platelet count tends to be low and drops even more in later stages of CNL. It also drops as the spleen and liver get bigger.
- **Elevated lactate dehydrogenase (LDH) level** — LDH is an enzyme found in all normal and abnormal cells. An increased LDH level may be a sign of CNL. It may also be a sign of tissue damage, other 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. People with CNL, chronic inflammation, certain types of cancer, or other medical conditions might have high LAP levels.

Other Tests. Lab tests called "karyotyping" and "cytogenetic analysis" are used to look for certain changes in chromosomes and genes. Molecular testing called "polymerase chain reaction"' (PCR) or "fluorescence in situ hybridization" (FISH) may also be done. These tests can find certain gene changes that are linked to different types of MPN and can help with diagnosis.

Visit www.LLS.org/booklets to view *Understanding Lab and Imaging Tests* for more information.

Chromosomal and Gene Mutations. Most CNL patients don't have chromosome abnormalities in their cells when they're diagnosed with CNL. The most common abnormalities, called "mutations," reported in a few case studies included trisomy 8, trisomy 21, del (20q), and del (11q).

***CSF3R* mutation.** Progress has been made in understanding the molecular basis of CNL with the discovery of the *CSF3R* gene, the receptor for colony-stimulating factor 3. Colony-stimulating factor 3 is the primary growth factor of neutrophil production.

Most CNL patients (possibly up to 90%) carry the *CSF3R* mutation. The *CSF3R* gene mutation falls into two categories: truncation mutations and membrane proximal mutations. Each of these responds to certain targeted therapy drugs already used to treat other kinds of cancer. Understanding the mutation can help doctors diagnose the disease and provide a target for therapy.

Other mutations. A small number of studies have found other gene mutations in some CNL patients; these mutations include *ASXL1, SETBP1, SRSF2, TET2, JAK2* and *CALR* mutations. More research is needed to find out if these mutations can help diagnose CNL, predict outcomes, and/or make treatment decisions.

Visit www.LLS.org/booklets to view *Understanding Genetics* for more information.

Treatment of Chronic Neutrophilic Leukemia (CNL)

There's no standard of care for CNL. Treatment focuses on managing symptoms rather than curing the disease. Once CNL progresses to acute myeloid leukemia (AML), there's only a slight chance of remission.

Allogeneic stem cell transplantation is the only potential cure for CNL.

Patients are advised to talk with their doctors about treatment options, including clinical trials (see page 4). It's important for the patient to see a hematologist-oncologist who has experience treating MPNs like CNL. Another option is going to a hematologist-oncologist who consults with a CNL expert at a major cancer center.

Drug Therapy for CNL. CNL is most often treated with hydroxyurea and other oral chemotherapy drugs. Interferon-alpha is also a treatment option. More recently, targeted therapy has been shown to help treat CNL.

Hydroxyurea is the chemotherapeutic drug that's most often used to treat CNL. It can help control high white blood cell counts and spleen enlargement until there's evidence of disease progression or blast transformation. When hydroxyurea stops working, other drugs including cladribine, thalidomide, and ruxolitinib (Jakafi®) have been used, but these tend to help only for a short time.

Interferon-alpha has been found to work in a few cases, where it has led to long-lasting responses. In some instances, it's been used on-and-off to treat progressive disease.

To date, complete remission using standard chemotherapy drugs has not been achieved.

Targeted therapy drugs might be used if the CNL cells have certain gene changes. For instance, patients with a *CSF3R* truncation mutation have been found to respond to a drug called dasatinib (Sprycel®). Patients with a *CSF3R* membrane proximal mutation may respond to ruxolitinib (Jakafi®). As more is learned about the genetics of CNL, other drugs may become treatment options.

Stem Cell Transplantation (SCT) for CNL. Because CNL often stops responding to the treatments used now and can transform into acute myeloid leukemia (AML), allogenic stem cell transplantation (SCT) is the only treatment that might cure this disease.

Allogeneic SCT has been used in a small number of cases to date. There are some reports of allogeneic SCT leading to long-lasting remission (ranging from a few months to several years). At this time, there's no information available on the use of other kinds of stem cell transplants (such as nonmyeloablative, cord-blood, or autologous) for CNL.

Visit www.LLS.org/booklets to view *Blood and Marrow Stem Cell Transplantation* for more information.

Clinical Trials for Blood Cancers

Every new cancer drug goes through a series of carefully controlled research studies before it can become part of standard cancer care. These research studies are called clinical trials and they are used to find better ways to care for and treat people with cancer.

In the United States, the FDA (US Food and Drug Administration) requires that all new drugs and other treatments be tested in clinical trials before they can be used. At any given time, there are thousands of cancer clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer.

Researchers use cancer clinical trials to study new ways to

- Treat cancer using:
  - A new drug
  - An approved drug to treat a different kind of cancer
  - A new combination of drugs
  - A new way of giving a drug – pill, intravenously (IV), etc.
- Manage cancer symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back (recurring) after treatment
- Manage long-term side effects

By taking part in a clinical trial, patients can see doctors who are experts in their disease, gain access to new, cutting-edge therapies, and provide helpful information for future patients. The treatments and information we have today are due in large part to patients being willing to join clinical trials. Anyone interested in being part of a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation it may help to:

- Have a list of questions to ask about the risks and benefits of each trial (visit www.LLS.org/WhatToAsk for lists of suggested questions).
- Ask a family member or friend to go with you when you see your doctor—both for support and to take notes.

Clinical trials can be difficult to understand and to navigate, but The Leukemia & Lymphoma Society is here to help. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find potential clinical trials, overcome the barriers to enrollment and provide support throughout the entire clinical trial process. Our Clinical Trial Nurse Navigators are registered nurses who are experts in blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will:

- Talk with you about your treatment goals
- Help you understand the clinical-trial process, including your rights as a patient
- Ask you for details about your diagnosis (such as past treatments, treatment responses, and your cancer genetic profile), your current health, and your medical history, because these might impact whether you can take part in certain clinical trials
- Help you understand how your finances, insurance coverage, support network, and ability and willingness to travel might impact your choice of clinical trials
- Guide and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites
- Help deal with any problems you might have as you enroll in a trial
- Support you throughout the clinical trial process

Please call an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials and the Clinical Trial Support Center at LLS.

Also, visit www.LLS.org/booklets to view *Understanding Clinical Trials for Blood Cancers*.

Outcomes for CNL Patients

The likely outcome of a disease, called the "prognosis," varies in patients with CNL. Individual factors including age, overall health, blood counts at time of diagnosis, gene changes found in the CNL cells, and response to treatment can all impact outcomes. For CNL, the reported median survival is about 24 months. Some people may survive much longer after diagnosis.

In general, statistics may underestimate survival rates 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. It cannot predict how any one person will respond.

The ongoing advances in the understanding of CNL are expected to improve treatment of the disease and 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 website 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

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 highly trained oncology social workers, nurses and health educators. They offer up-to-date disease, treatment and support information. Language services (interpreting and translation) are available. Please contact our Information Specialists or visit our website for more information:

- Call: (800) 955-4572 (Monday through Friday, from 9 am to 9 pm ET)
- Email and Live chat: www.LLS.org/InformationSpecialists

Clinical Trials Support Center (CTSC). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations provided by a registered dietitian who has experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition to schedule a consultation or to get more information.

Free Information Booklets. LLS offers free education and support booklets that can either be read online or ordered. Please visit www.LLS.org/booklets for more information.

LLS Health Manager™ App. This free mobile app helps you manage your health by tracking side effects, medication, food and hydration, questions for your doctor, and more. Export the information you've tracked in a calendar format and share it with your doctor. You can also set up reminders to take medications, hydrate, and eat. Visit www.LLS.org/HealthManager to download for free.

LLS Coloring for Kids™. This free coloring app allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. The app includes blank canvases, general coloring pages, and pages from LLS coloring books. This app can be used anywhere and may help pass the time in waiting rooms or during treatment. Visit www.LLS.org/ColoringApp to learn more and download.

Financial Assistance. LLS offers financial support including insurance premium and medication co-pay assistance, as well as travel and other needs, to eligible individuals with blood cancer. For more information, please:

- Call: (877) 557-2672
- Visit: www.LLS.org/finances

Información en Español (LLS information in Spanish). Please visit www.LLS.org/espanol for more information.

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

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit www.LLS.org/community to join.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients to reach out and share information. Please visit www.LLS.org/chat for more information.

Podcast. *The Bloodline* with LLS is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more information and to subscribe.

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), local 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

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. Please visit www.LLS.org/ResourceDirectory for more information.

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

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information please:

- Call: the VA at (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area, lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please:

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a 2-week period. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter "depression" in the search box

Other Resources

The Myeloproliferative Disorders Research Consortium (MPD-RC)
https://icahn.mssm.edu/about/departments/medicine/research-office/medicine/myeloprofilerative

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 (NIH), is a national resource center for information and education about all forms of cancer, including CNL.

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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