LEUKEMIA & LYMPHOMA SOCIETY®

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# Chronic Myeloid Leukemia

Revised **2019**

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## A six-word narrative about living with blood cancer from patients in our LLS Community

**Stay strong and keep moving forward. Find the positive in every day. Be your own best patient advocate. Changed my life for the better. Accept, learn and focus on present. Learning to live a different life. Sudden and life changing—be positive. Waiting, worrying, anxiousness/ happy I'm alive! Embrace a new normal each day. 5 years, 41 infusions, constant fatigue. Patience, positive attitude, hope and faith. Test to test, I will survive! Treatment, fatigue, treatment, fatigue and survival. Love life, live better every day. I don't look back only forward. So far, so good, live life. Meditation, mindfulness, wellness, faith, nutrition and optimism. Finding the joy while living with uncertainty. Watch, wait, treat, regroup, rest, re-energize. Blessed to be doing so well! Eye opening needed learning and healing. Feel great: uncertain travel plans annoying. Renewed faith, meditation, diet, mindfulness, gratitude. Watchful waiting can be watchful worrying. Scary, expensive, grateful, blessings, hope, faith. Thank god for stem cell transplants! Do not know what to expect. Extraordinarily grateful, I love my life. Diagnosed; frightened; tested; treating; waiting; hoping. I'm more generous, impatient less often. Embrace your treatment day after day. Live today, accept tomorrow, forget yesterday. Strength you never realized you had. Challenging to our hearts and minds. Life is what we make it. Live life in a beautiful way.**

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Join our online social network for people who are living with or supporting someone who has a blood cancer. Members will find

- **Thousands of patients and caregivers sharing experiences and information, with support from knowledgeable staff**
- **Accurate and cutting-edge disease updates**
- **The opportunity to participate in surveys that will help improve care.**

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## Acknowledgements

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# Introduction

Chronic myeloid leukemia (CML), also known as chronic myelogenous leukemia, is a type of cancer that starts in the blood-forming cells of the bone marrow and invades the blood.

Approximately 8,990 new cases of CML are expected to be diagnosed in 2019. As of 2015, the latest year for which statistics are available, an estimated 50,948 people are either living with or in remission from CML.[1] See *Incidence, Causes and Risk Factors* on *page 40*.

Since the introduction of tyrosine kinase inhibitor (TKI) therapy in 2001, CML has been transformed from a life-threatening disease to a manageable chronic condition for most patients. People with CML are living longer and experiencing fewer treatment side effects, and the possibility of discontinuing treatment is now feasible for select patients in remission who meet specific criteria.

The more you know about your disease, the better you can take care of yourself—your mind, your body and your health. This booklet provides information about CML, defines complicated terms, provides information about normal blood and bone marrow, explains tests and treatments for CML and lists new research options and clinical trials.

We trust that the information in this booklet will provide you with a good working knowledge of CML, or that it will reinforce what you already know. We hope you keep this booklet handy. Should you ever feel alone in confronting problems, we hope you will turn to it for information, guidance and assistance in locating the support and resources that you need.

We are here to help.

[1] Source: *Facts 2018-2019*. The Leukemia and Lymphoma Society. April 2019.

# Leukemia

Leukemia is a cancer that starts in the blood-forming cells in the bone marrow. Bone marrow is the sponge-like tissue in the center of most bones. It produces red blood cells, white blood cells and platelets. In leukemia, cancerous blood cells form and crowd out healthy blood cells in the bone marrow. The four major types of leukemia are

- Acute myeloid leukemia (AML)
- Chronic myeloid leukemia (CML)
- Acute lymphoblastic leukemia (ALL)
- Chronic lymphocytic leukemia (CLL).

Leukemia is classified as either “acute” or “chronic.” These two terms describe how quickly the disease progresses in the absence of treatment. Acute forms of leukemia progress rapidly and produce cells that are not fully developed. These immature cells cannot perform their normal functions. Chronic forms of leukemia usually progress slowly, and patients have greater numbers of mature cells. In general, these more mature cells can carry out some or all of their normal functions. See *Normal Blood and Bone Marrow* on *page 41*.

Leukemia is further classified by the type of white blood cell, either “myeloid” or “lymphoid,” that becomes cancerous. The name of each of the four types of leukemia describes whether the disease progresses quickly (acute) or slowly (chronic) and identifies the type of white blood cell that is involved (myeloid or lymphoid).

# What Is CML?

Chronic myeloid leukemia (CML) is a type of leukemia that progresses slowly (is chronic) and involves the myeloid white blood cells in the bone marrow. It is known by several other names, including

- Chronic myelogenous leukemia
- Chronic granulocytic leukemia
- Chronic myelocytic leukemia

CML is classified by the World Health Organization (WHO) as a “myeloproliferative neoplasm.” This is a type of disease in which the bone marrow makes too many white blood cells. As the number of extra cells build up in the blood and/or bone marrow, this disease usually gets worse slowly over time. This increased accumulation of cells may eventually cause anemia, fatigue, bleeding and other problems.

**Visit www.LLS.org/booklets to reach the free LLS booklet *The CML Guide: Information for Patients and Caregivers.***

**The Philadelphia Chromosome and the *BCR-ABL1* Fusion Gene.** A chromosome is an organized package of DNA found in the nucleus of a cell. Human cells normally contain 23 pairs of chromosomes (46 total): each pair looks different from the others and is identified by a number. Chromosome pairs are made up of one chromosome from each parent. Twenty-two of these pairs are called “autosomes,” and they look the same in both males and females. The 23rd pair consists of the sex chromosomes, which are different for males and females. The pair in males is made up of one X chromosome and one Y chromosome, while the pair in females is made up of two X chromosomes.

Cells in the body have to make new copies of themselves to replace worn-out cells. To make a new copy of itself, a cell duplicates all of its contents, including its chromosomes, and then splits to form two cells. Sometimes errors occur during the process of a cell copying itself or dividing into new cells. One type of error is called a "translocation." A translocation occurs when a piece of one chromosome breaks off and attaches to another chromosome. This can result in a "fusion gene," an abnormal gene that is formed when two different genes are fused together.

All cases of CML are caused by the *BCR-ABL1* fusion gene. This gene is not found in normal blood cells. The *BCR-ABL1* gene is formed by a translocation between parts of chromosomes 9 and 22 in a single bone marrow cell during cell division. Part of chromosome 9 attaches to chromosome 22, and part of chromosome 22 attaches to chromosome 9, resulting in a longer-than-normal chromosome 9 and a shorter-than-normal chromosome 22. The abnormal chromosome 22 is known as the "Philadelphia chromosome" (so called because it was discovered at the Wistar Institute in Philadelphia). "Ph" is the abbreviation for the Philadelphia chromosome. The Ph abbreviation with a "plus" sign (Ph+) indicates the presence of the abnormal Ph chromosome. A Ph abbreviation with a "negative" sign (Ph-) indicates that the Ph chromosome is not detected in the disease cells (see **Figure 1** on *page 5*).

The short piece of chromosome 9 has the *ABL1* gene (named for the scientist who discovered this gene, Herbert Abelson). The break on chromosome 22 involves a gene called "*BCR*" (breakpoint cluster region). Part of the *ABL1* gene moves to chromosome 22 and fuses with the first portion of the *BCR* gene. The result of this fusion is the leukemia-causing gene, called *BCR-ABL1* (see **Figure 2** on *page 6*).

Genes provide cells with instructions for making proteins. The *ABL1* gene instructs the cell to make a protein called a "tyrosine kinase." This protein sends signals that tell cells when to grow and divide. The abnormal *BCR-ABL1* gene produces an abnormal protein called "BCR-ABL1 tyrosine kinase." This abnormal protein displays an unusually high level of tyrosine kinase activity and signals blood stem cells to produce too many granulocytes (white blood cells). These granulocytes have the *BCR-ABL1* gene and are therefore "leukemia cells" or "CML cells." These granulocytes are not completely normal and do not become healthy white blood cells. They make new cells too quickly. Over time, additional mutations occur in some of the CML cells, which results in the cells not maturing to become normal white blood cells. Immature cells build up in the bone marrow and crowd out healthy red blood cells, white blood cells and platelets. As a result, anemia, infection or excessive bleeding may occur. This is known as the "blast crisis" phase. See *Phases of CML and Prognostic Factors* on *page 9*.

More than 95 percent of CML patients have the Philadelphia chromosome. This is called Ph+ CML. However, a very small number of CML patients have the *BCR-ABL1* gene but no detectable Philadelphia chromosome. This is called Ph negative (Ph–) CML. Patients with CML who have the *BCR-ABL1* gene rearrangement but are Ph- have the same prognosis (likely outcome) as Ph+ patients.

Some patients have a type of leukemia in which too many granulocytes are made in the bone marrow. However, these patients are Ph— and do not have the *BCR-ABL1* gene. They may be diagnosed as having "atypical CML." This means there may be other, unknown oncogenes that caused the disease in these patients. These patients generally have poorer responses to treatment and shorter survival times.

## Figure 1. Marrow Cell Chromosomes

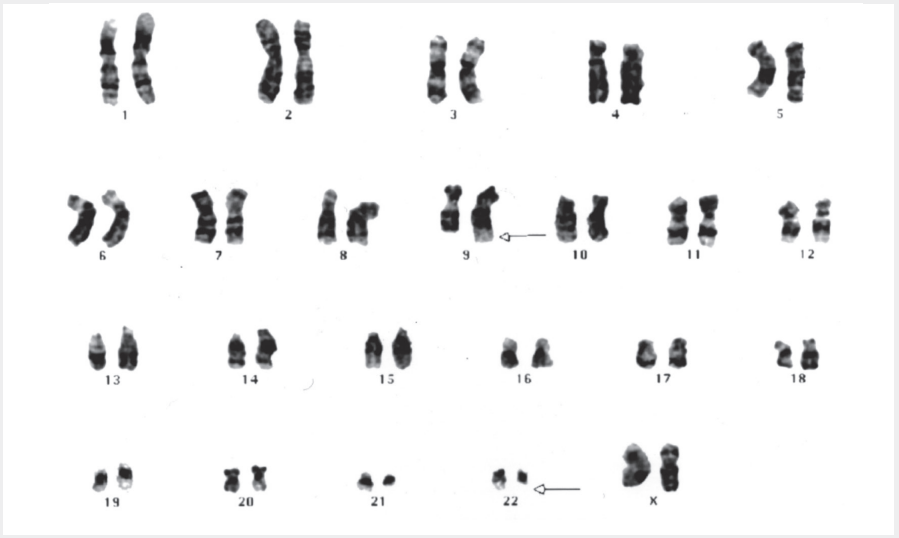


**Figure 1.** Shown here is the set of chromosomes from a marrow cell of a female patient with CML. The higher the chromosome number, the smaller the chromosome. The arrow in the fourth row indicates the shortened arm of chromosome 22 (the Ph chromosome), characteristic of the leukemic marrow cells of patients with CML. The arrow in the second row indicates chromosome 9, which is elongated. These two changes reflect the translocation of chromosome material between chromosomes 9 and 22.

*This figure kindly provided by Nancy Wang, PhD, University of Rochester Medical Center, Rochester, NY.*

**Figure 2. Chronic Myeloid Leukemia-Causing Event—How the *BCR-ABL1* Cancer-Causing Gene (Oncogene) Is Formed**

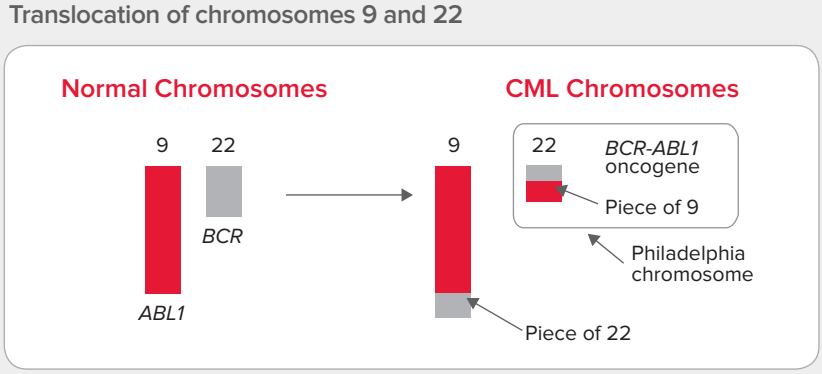


**Figure 2.**

- A portion of the *ABL1* gene from chromosome 9 translocates and fuses with the remaining portion of the *BCR* gene on chromosome 22. The translocated piece of chromosome 9 results in a fusion gene called *BCR-ABL1*.
- The *BCR-ABL1* fusion gene directs the production of an abnormal (mutant) protein, an enzyme called BCR-ABL1 tyrosine kinase (see **Figure 3** on *page 9*).
- The abnormal enzyme protein is the principal factor in converting the marrow stem cell from a normal cell into a leukemic cell.

# Signs and Symptoms

Unlike other forms of leukemia, CML is a slow-growing disease and does not completely interfere with the development of red blood cells, white blood cells and platelets. Therefore, patients may have CML but have no signs or symptoms. Those with symptoms often report experiencing

- Weakness
- Fatigue
- Shortness of breath during basic everyday activities
- Fever
- Bone pain
- Unexplained weight loss

- Pain or a feeling of fullness below the ribs on the left side, due to an enlarged spleen
- Night sweats

Many of the signs and symptoms occur because the CML cells crowd out the bone marrow's healthy red blood cells, white blood cells and platelets.

Anemia is a shortage of red blood cells that can cause weakness, fatigue and shortness of breath. A shortage of normal white blood cells can increase the risk of infection in CML patients and a shortage of platelets can lead to excessive bruising or bleeding. Symptoms may also occur because CML cells collect in organs such as the spleen.

# Diagnosis

Many people with CML do not have symptoms when diagnosed. The most common sign of CML is an abnormal white blood cell count, often found during blood tests for an unrelated health problem or during a routine checkup.

To diagnose CML, doctors use a variety of tests to analyze blood and bone marrow cells. A pathologist—a doctor who specializes in identifying diseases by studying cells under a microscope—will examine the blood cells and the bone marrow cells. The samples should also be examined by a hematopathologist, a specialist who diagnoses diseases of the blood and marrow.

The following are some of the tests done to diagnose CML.

**Complete Blood Count (CBC) with Differential.** This test is used to measure the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin (a protein in red blood cells that carries oxygen) in the red blood cells and the percentage of red blood cells in the sample. The CBC should include a differential, which measures the different types of white blood cells in the sample. People with CML often have

- An increased white blood cell count, often very high levels
- A decreased red blood cell count
- The possibility of increased or decreased platelet counts depending on the severity of the disease

**Peripheral Blood Smear.** In this test, blood cell samples are stained (dyed) and examined with an optical microscope. These samples show

- The number, size, shape and type of blood cells
- The specific pattern of white blood cells

- The proportion of immature cells (blast cells) compared to the proportion of maturing and fully matured white blood cells.

Blast cells are not normally present in the blood of healthy individuals.

**Bone Marrow Aspiration and Biopsy.** These tests are used to examine bone marrow cells to find abnormalities and are generally done at the same time. In both cases, after medicine has been given to numb the skin, a needle is inserted into the patient's hip bone. For a bone marrow aspiration, the needle is inserted into the bone marrow to remove a liquid sample of cells. For a bone marrow biopsy, the needle removes a small sample of bone that contains marrow. Both samples are examined under a microscope to look for chromosomal and other cell changes.

**Cytogenetic Analysis.** Cytogenetics is the study of chromosomes and chromosomal abnormalities. Samples from the bone marrow are examined under a microscope for chromosomal changes or abnormalities, such as the Philadelphia (Ph) chromosome. The presence of the Ph chromosome in the bone marrow cells, along with a high white blood cell count and other characteristic blood and bone marrow test findings, confirm the diagnosis of CML. In about 95 percent of people with CML, the Ph chromosome in bone marrow cells is detectable by cytogenetic analysis. In a small percentage of people with clinical signs of CML, the Ph chromosome cannot be detected by cytogenetic analysis. However, they almost always test positive for the *BCR-ABL1* fusion gene on chromosome 22, found with the other types of tests listed below.

**FISH (fluorescence in situ hybridization).** FISH is a laboratory test used to examine genes and chromosomes in cells. FISH is a slightly more sensitive method for detecting CML than the standard cytogenetic tests that identify the Ph chromosome. FISH can identify the presence of the *BCR-ABL1* gene (see **Figure 3** on *page 9*). Genes are made up of DNA segments. FISH uses color probes that bind to DNA to locate the *BCR* and *ABL1* genes in chromosomes. The *BCR* and *ABL1* genes are labeled with two different chemicals, each of which releases a different color. The color shows up on the chromosome that contains the gene—normally chromosome 9 for *ABL1* and chromosome 22 for *BCR*—so FISH can detect the piece of chromosome 9 that has moved to chromosome 22 in CML cells. The *BCR-ABL1* fusion gene is shown by the overlapping colors of the two probes.

**Figure 3. Identifying the *BCR-ABL1* Gene Using FISH**

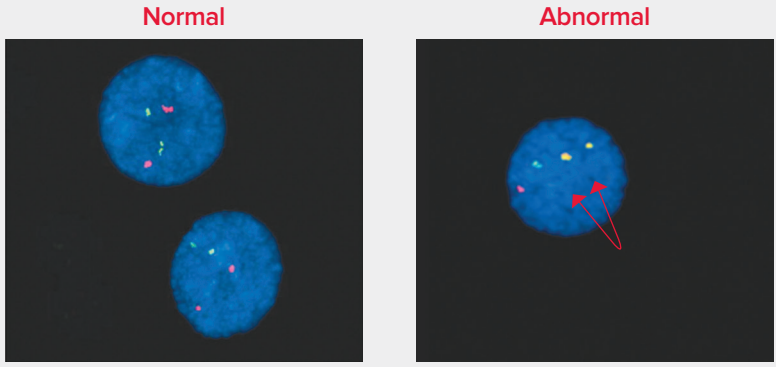


**Figure 3.** Fluorescence in situ hybridization, or FISH, is a testing method that uses fluorescent molecules to mark the *BCR-ABL1* gene in CML. In normal cells, two red and two green signals indicate the location of the normal *ABL1* and *BCR* genes, respectively. In abnormal cells, the fusion of *BCR* and *ABL1* is visualized through the fusion of the red and green signals. It is frequently detected as a yellow fluorescence (indicated above by arrows).

**Quantitative Polymerase Chain Reaction (qPCR).** The qPCR test is the most sensitive test that detects and measures the quantity of the *BCR-ABL1* gene in blood or bone marrow samples. It can detect very small amounts of the *BCR-ABL1* gene (even when the Ph chromosome cannot be detected in blood or bone marrow cells with cytogenetic testing), to a level of one CML cell among 100,000 to 1,000,000 normal cells.

Blood cell counts, bone marrow examinations, FISH and qPCR may also be used to monitor a person's response to therapy once treatment has begun. A qPCR test is recommended every 3 months initially. Even for patients with relatively deep remissions lasting at least 2 years, the test should continue to be done every 3 to 6 months.

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# Phases of CML and Prognostic Factors

For most types of cancer, doctors assign a "stage" based on the size of the tumor and whether the cancer has spread to the lymph nodes or other parts of the body. The doctor takes the patient's stage into account when determining a prognosis (likely outcome) and planning treatment. However, CML is not staged in the same way as most cancers. Instead, CML is categorized into three groups, called "phases." Knowing the phase of CML helps doctors determine appropriate treatment and predict a patient's prognosis.

The three phases of CML are

- Chronic phase
- Accelerated phase
- Blast phase (also called “blast crisis phase”)

Doctors use diagnostic tests to determine the phase of CML. Determing the CML phase is based primarily on the number of immature white blood cells (blasts) in the patient’s blood and bone marrow. There are three different staging classification systems for CML. Each of them uses slightly different percentages of blast cells to define the phases. These differences apply to definitions of accelerated and blast phases, but they do not have practical disease management implications in most cases.

**Chronic Phase.** Most patients are diagnosed with CML in the chronic phase of the disease. People with chronic phase CML

- May or may not have symptoms
- Have an increased number of white blood cells
- Usually respond well to standard treatment
  - Specifically, symptoms go away, white blood cell counts return to normal levels, hemoglobin concentration improves and the spleen reduces in size.

If untreated, chronic phase CML will eventually progress to accelerated phase and/or blast phase CML.

**Accelerated Phase.** In the accelerated phase, the number of immature myeloid blast cells has risen, and sometimes new chromosomal changes, in addition to the Ph chromosome, occur.

People with accelerated phase CML may have

- More than 20 percent basophils (type of white blood cell) in the bloodstream
- More than 20 percent blasts in the blood and bone marrow
- Low platelet counts unrelated to therapy
- Increased spleen size
- Worsening anemia (caused by low levels of red blood cells)
- Additional chromosome abnormalities in the CML cells

In the accelerated phase, the number of CML cells grows faster and causes symptoms such as fatigue, fever, weight loss and an enlarged spleen. If untreated, accelerated phase CML will eventually transform into blast phase CML.

**Blast Phase (Also Called "Blast Crisis Phase").** The blast phase looks and behaves like the acute form of myeloid leukemia.

People who have blast phase CML may have

- Anemia
- A very high white blood cell count
- Very high or very low platelet counts
- Blast cells that have spread outside the blood and/or the bone marrow to other tissues and organs
- CML cells with new chromosome abnormalities
- Symptoms such as
  - Fever
  - Fatigue
  - Shortness of breath
  - Abdominal pain
  - Bone pain
  - Enlarged spleen
  - Poor appetite and weight loss
  - Bleeding
  - Infections

**Prognostic Factors.** There are other factors in addition to the phase of CML that affect treatment decisions and predict a patient's prognosis (likely outcome). These are known as prognostic factors. The following are prognostic factors for patients with CML at the time of diagnosis and also indicate when the likely outcome is less favorable:

- Phase of CML—Patients who have accelerated or blast phase CML have a less favorable prognosis than those who have chronic phase CML.
- Age—Patients age 60 years and older have a less favorable prognosis.
- Spleen size—Patients with an enlarged spleen have a less favorable prognosis.
- Platelet count—Patients who have very high or very low platelet counts at diagnosis have a less favorable prognosis.
- Blasts in the blood—Patients who have a high number of blasts in the blood have a less favorable prognosis.
- Increased numbers of basophils and eosinophils in the blood—Patients with increased numbers of these types of white blood cells have a less favorable prognosis.

Many of these factors are used in prognostic scoring systems to predict the outcome for patients with CML. Currently, there are three prognostic scoring systems used to determine a patient's risk at the time of diagnosis.

- The Sokal score is based on the patient's age, spleen size, platelet count and the percentage of blast cells and basophils circulating in the peripheral blood (blood circulating throughout the body).
- The Hasford score uses the same factors as the Sokal system, but it also includes the number of eosinophils and basophils circulating in the peripheral bloodstream.
- The European Treatment and Outcome Study (EUTOS) score uses only the percentage of basophils circulating in the peripheral bloodstream and spleen size.

See the section entitled *More Information* on *page 56* for links to these scoring systems.

Doctors use risk scores to help determine treatment decisions. The Sokal and Hasford systems categorize patients into three groups (low-risk, intermediate-risk and high-risk) whereas the EUTOS score categorizes patients into only two groups (low-risk or high-risk). Generally, a low-risk CML patient is likely to have a better response to treatment.

# Treatments for CML

New treatments may have been approved since this book was printed.
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Doctors who specialize in treating patients with CML are called "hematologist-oncologists." A hematologist-oncologist is a doctor who has special training in diagnosing and treating blood cancers, such as leukemia, lymphoma and myeloma. These doctors can determine the most appropriate treatment options for each patient.

Until recently, it was believed that CML could not be cured with current drug therapies. But over time, more and more CML patients are achieving extremely deep remissions. Some of these patients have been able to successfully discontinue treatment with careful molecular monitoring. With current drug therapies, most people diagnosed with chronic phase CML can expect to have good quality of life for a normal lifespan.

The treatment of CML has improved significantly since the introduction of tyrosine kinase inhibitors (TKIs). This included approval of imatinib mesylate (Gleevec®), the first-generation TKI, in 2001; approval of the second-generation TKIs, including dasatinib (Sprycel®) in 2006, nilotinib (Tasigna®) in 2007 and bosutinib (Bosulif®) in 2012; and approval of ponatinib (Iclusig®), the third-generation TKI, in 2012. The introduction of TKIs changed CML from a potentially fatal disorder to one that can be controlled. However, not all patients respond to TKIs, and some patients develop resistance to these drugs.

A generic drug is a medication created to be the same as an already marketed brand-name drug in terms of dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. These similarities help to demonstrate bioequivalence, which means that a generic medicine works in the same way and provides the same clinical benefit as its brand-name version. In other words, you can take a generic medicine as an equal substitute for its brand-name counterpart. The US Food and Drug Administration (FDA) employs strict standards to ensure that generic drugs are bioequivalent to brand name drugs in the US.

The approach for treating each patient and the choice of treatment is based on the phase of CML at diagnosis, risk scores, age and the patient's other health issues. For a list of drugs used to treat CML, see **Table 1** on *page 22*.

**Lowering High White Blood Cell Counts.** Some patients have very high white blood cell (WBC) counts at the time of diagnosis. These elevated WBC counts can sometimes impair blood flow to the brain, lungs, eyes and other sites, and also cause damage in small blood vessels.

**Hydroxyurea (Hydrea®)** is sometimes given to lower very high WBC counts rapidly, until a suspected CML diagnosis can be confirmed through blood and bone marrow tests. Hydroxyurea is taken as a capsule by mouth. Hydroxyurea can help reduce the size of the spleen. Once a diagnosis of CML is confirmed, doctors usually start TKI therapy and discontinue hydroxyurea.

Leukapheresis is a procedure that uses a machine similar to a dialysis machine to remove white blood cells from the circulating blood. Leukapheresis is used to lower WBC counts in female patients diagnosed with chronic phase CML during the first months of pregnancy, when other treatments may be harmful to fetal development, or to immediately reduce a dangerously high WBC count. For more information about fertility and pregnancy, see *page 35*.

**Tyrosine Kinase Inhibitor Therapy.** Tyrosine kinase inhibitors (TKIs) are a type of targeted therapy taken orally as pills. Targeted therapies identify and attack specific types of cancer cells while causing less damage to normal cells than conventional treatments. In CML, TKIs target the abnormal BCR-ABL1 protein that causes uncontrolled CML cell growth and block this abnormal protein's ability to function, causing the CML cells to die.

The first therapy given for a disease is called "initial" treatment. Four TKI drugs are approved as initial therapy (first-line treatment) for chronic phase CML:

- Imatinib mesylate (Gleevec®)
- Dasatinib (Sprycel®)
- Nilotinib (Tasigna®)
- Bosutinib (Bosulif®)

The first treatment may not work because of intolerance to a particular drug (intolerable side effects) or because of drug resistance (meaning the disease does not respond to the drug). When an initial treatment does not work, a second treatment option is tried. If both the initial treatment and the subsequent treatment (second-line) fail to work, a third treatment option (third-line) can be offered to the patient. In the case of resistance and/or intolerance to second-line treatments, another TKI option for treatment is ponatinib (Iclusig®).

Patients with a history of cardiac disease or peripheral vascular disease need to be monitored carefully and frequently during TKI treatment. It is rare, but some patients treated with TKIs have developed serious cardiac side effects, including congestive heart failure and QT interval prolongation (changes in heartbeat rhythm). Many patients who develop adverse cardiac effects also have other health problems and risk factors, including older age and a medical history of cardiac disease.

**Imatinib mesylate (Gleevec)**

- In 2001, the Food and Drug Administration (FDA) approved imatinib as the first TKI treatment for CML. Because imatinib was the first TKI, it is known as a "first-generation" TKI.
- This highly effective oral drug therapy brings about a stable remission in the majority of people with chronic phase CML.
- Imatinib has been a standard initial therapy (first-line treatment) for chronic phase CML since 2001.
- The FDA has approved imatinib to treat
  - Newly diagnosed adult and pediatric patients with Ph+ CML in chronic phase
  - Adults with Ph+ CML in blast crisis, accelerated phase or chronic phase after failure of interferon-alpha therapy
- Imatinib should be taken with a meal and a large glass of water.
- The drug is generally well tolerated by the majority of both younger and older patients, although most people experience some side effects. It is important for patients to tell their doctors about any side effects, because most of them can be managed. Common side effects of imatinib are
  - Nausea, vomiting and/or diarrhea
  - Muscle cramps and bone pain
  - Fatigue
  - Rashes
- Although rare, serious side effects of imatinib include
  - Low blood counts. Having low numbers of red blood cells, white blood cells and platelets can increase a patient's risk of anemia, infection and/or bleeding.

- Edema (fluid retention—swelling around the eyes, feet, lungs or heart)
- Congestive heart failure (impaired ability of the heart to pump blood) and left ventricular dysfunction (impaired functioning of the left side of the heart), particularly in patients with other health issues and risk factors. Patients with heart disease or risk factors for heart disease should be monitored and treated for this condition.
- Severe liver problems

- Some CML patients are not able to tolerate the side effects of imatinib. For other patients imatinib stops working, which is known as "imatinib resistance." In some cases, patients can overcome imatinib resistance by increasing the dose of imatinib. Other patients, however, may need to take a different TKI. Fortunately, there are other approved therapies for people with imatinib intolerance or resistance. When imatinib is not a treatment option, doctors decide, along with their patients, which of the other treatment options is the best alternative.

**Dasatinib (Sprycel)**

- Dasatinib was initially approved by the FDA in 2006. Because dasatinib was developed after imatinib, it is called a "second-generation" TKI.
- The FDA has approved dasatinib to treat adults with
  - Newly diagnosed Ph+ CML in chronic phase
  - Chronic, accelerated or blast phase Ph+ CML with either resistance to or intolerance of other treatments (including imatinib)
- In 2017, dasatinib was approved by the FDA to include treatment for pediatric patients with CML in chronic phase.
- Dasatinib is taken once daily, either in the morning or evening, with or without food. Patients taking an antacid medicine should take it either 2 hours before or 2 hours after taking dasatinib.
- Grapefruit products may increase the amount of dasatinib in the blood. Patients should avoid grapefruit, grapefruit juice and any supplement containing grapefruit extract while taking dasatinib.
- Studies of dasatinib have shown that it is more potent than imatinib and it induces faster and deeper molecular responses. To date, dasatinib has not been shown to increase survival compared to imatinib.
- Common side effects of dasatinib include
  - Nausea
  - Diarrhea
  - Headache
  - Fatigue
  - Shortness of breath

- Rash
- Fever

- Dasatinib may cause serious side effects, including
  - Low blood cell counts. Having low numbers of red blood cells, white blood cells and platelets increase a patient's risk of anemia, infection and/or bleeding.
  - Fluid retention around the lungs, the heart or stomach. Patients should call the doctor immediately if they get any of these symptoms: swelling all over the body, weight gain, shortness of breath and cough (especially during low levels of physical activity or at rest) and chest pain when taking a deep breath.
  - Rarely, an increased risk of a serious condition called pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of the lungs. Doctors should check the heart and lungs of patients both before and during treatment with dasatinib. If a patient is diagnosed with PAH while taking dasatinib, the medication should be discontinued permanently. PAH may be reversible after dasatinib is discontinued.

**Nilotinib (Tasigna)**

- Nilotinib is a second-generation TKI approved by the FDA in 2007 to treat CML, and is approved for
  - Newly diagnosed adults with Ph+ CML in chronic phase
  - Adults with Ph+ CML in chronic phase and accelerated phase who are resistant to or intolerant of prior therapy (including imatinib)
- In 2018, nilotinib was also approved for pediatric patients age 1 and older who
  - Are newly diagnosed and in chronic phase
  - Have resistance to or intolerance of prior TKI therapy
- Grapefruit products increase the amount of nilotinib in the blood. This may increase a patient's chance for serious and life-threatening side effects. Patients should avoid grapefruit, grapefruit juice and any supplement containing grapefruit extract while taking nilotinib.
- Nilotinib is usually taken twice a day. It should be taken on an empty stomach. Patients should avoid eating food for at least 2 hours before and also at least 1 hour after the dose is taken.
- Studies have shown that nilotinib is more potent than imatinib and that it induces faster and deeper molecular responses. To date, nilotinib has not been shown to increase survival compared to imatinib.

- One serious side effect of nilotinib is that it may cause heart rhythm problems in some patients. This is sometimes caused by nilotinib interacting with other drugs or supplements, so it is very important for patients to tell their doctors about any supplements or medicines, including over-the-counter medicines they are taking.
- Patients who take histamine type 2 receptor antagonists/blockers (called H2 blockers) should take these medicines about 10 hours before or about 2 hours after taking nilotinib. Patients taking antacids containing aluminum hydroxide, magnesium hydroxide or simethicone should take these medicines about 2 hours before or about 2 hours after taking nilotinib.
- Common side effects include
  - Nausea, vomiting, diarrhea
  - Rash
  - Headache
  - Fatigue
  - Itching
  - Cough
  - Constipation
  - Muscle and joint pain
  - Runny or stuffy nose, sneezing, sore throat
  - Fever
  - Night sweats
- Serious side effects of nilotinib include
  - Low blood cell counts. Having low numbers of red blood cells, white blood cells and platelets can increase a patient's risk of anemia, infection and/or bleeding.
  - QT interval prolongation, a serious heart problem that causes a change in heartbeat rhythm that can be fatal. The patient should contact the doctor immediately if he or she feels lightheaded, faint or has an irregular heartbeat while taking nilotinib. Before starting nilotinib and during treatment with nilotinib, the doctor should check the patient's heart with a test called an electrocardiogram (ECG).
  - Blood clots or blockages in blood vessels (arteries), which can cause decreased blood flow to the leg, heart or brain
  - Liver damage symptoms, including yellow skin and eyes ("jaundice")
  - Inflammation of the pancreas. Symptoms include stomach pain with nausea and vomiting.

- Hyperglycemia, a higher-than-normal amount of glucose (sugar) in the blood
- Fluid retention. Symptoms include shortness of breath, rapid weight gain and swelling.

**Bosutinib (Bosulif)**

- Bosutinib is a second-generation TKI that was approved by the FDA in 2012 to treat adults with chronic, accelerated or blast phase Ph+ CML with resistance to or intolerance of prior therapy.
- In 2017, bosutinib's FDA approval was expanded to include treatment of adult patients with newly-diagnosed chronic phase Ph+ CML.
- Side effects include
  - Stomach pain, diarrhea, nausea and/or vomiting
  - Fluid retention
  - Rash
  - Fatigue
- Serious side effects include
  - Low blood cell counts. Having low numbers of red blood cells, white blood cells and platelets can increase a patient's risk of anemia, infection and/or bleeding.
  - Liver problems
  - Fluid retention around the lungs, heart and stomach
  - Kidney problems

**Ponatinib (Iclusig)**

- The FDA approved ponatinib to treat CML in 2012. Ponatinib is a third-generation TKI approved for
  - Adult patients in chronic, accelerated or blast phase CML for whom no other TKI is indicated
  - Adult patients with the T315I mutation in chronic, accelerated or blast phase CML
- Ponatinib may be taken either with or without food.
- Ponatinib targets all the changes (mutations) on the BCR-ABL1 protein that are resistant to imatinib and other TKIs. However, this drug can cause severe side effects and is not a good option for all patients.

- The most common side effects include
  - Skin rash
  - Stomach-area (abdominal) pain
  - Fatigue
  - Headache
  - Dry skin
  - Fever
  - Constipation
  - High blood pressure
- Serious or life-threatening risks include
  - Blood clots or blockages in blood vessels (arteries and veins). Patients should get medical help right away if they have any of the following symptoms: chest pain or pressure; pain in the arms, legs, back, neck or jaw; shortness of breath; numbness or weakness on one side of the body; leg swelling; headache; severe stomach pain; dizziness; decreased vision or loss of vision; and/or trouble talking.
  - Heart problems, including heart failure, irregular, slow or fast heartbeats and heart attack. Doctors will check patients' heart function, both before and during treatment with ponatinib. Patients with cardiovascular risk factors should be referred to a cardiologist. Get medical help right away if you have any of the following symptoms: shortness of breath, chest pain, fast or irregular heartbeats, dizziness or feeling faint.
  - Liver problems, including liver failure. Symptoms may include yellowing of the skin or white part of the eyes (jaundice), dark-colored urine, bleeding or bruising, loss of appetite and sleepiness.
- Other serious side effects include
  - High blood pressure
  - Pancreatitis (inflammation of the pancreas)
  - Neuropathy (damage to the nerves in the arms, brain, hands, legs or feet)
  - Serious eye problems that can lead to blindness or blurred vision
  - Severe bleeding
  - Fluid retention

**Drug Interactions.** The way TKIs work in the body can be affected by certain drugs, herbal supplements and even some foods. Corticosteroids, anti-seizure medication, antacids and the herbal supplement St. John's Wort can make some TKIs less effective. Some products may increase the amount of TKIs in the blood to high, unsafe levels; these include certain antibiotics, antifungal medications and grapefruit products.

TKIs can have serious or even deadly interactions with other prescription medications, over-the-counter medications, supplements and even certain foods. Patients should always provide their doctors with a list of any medications, herbal supplements and vitamins they are taking to be certain that it is safe to take these products while taking the TKIs. It is also important to ask the doctor about any foods that should be avoided.

**TKI Resistance.** "Treatment response" is the term used to describe an improvement in a disease that can be attributed to treatment. "Drug resistance" is the term used when a disease has not responded to treatment. Drug resistance in CML occurs when cancer cells do not respond to a drug that is being used to kill or weaken the cancer.

"Primary resistance" is the term that describes resistance to a drug that is being taken for the first time in the disease process. "Secondary resistance" occurs when cancer cells initially respond to a treatment but then stop responding. In CML, resistance is often caused by mutations in the *BCR-ABL1* gene. These mutations alter the shape of the BCR-ABL1 protein, which can affect the blocking action of the TKI on *BCR-ABL1,* allowing cancer cells to grow again. Sometimes, resistance to a TKI can be stopped by increasing the dose of the drug or by switching to another type of TKI. Second-generation TKIs can be effective in treating patients with mutations that are resistant to imatinib. *BCR-ABL1* kinase domain mutation analysis is a test that identifies the mutations in the *BCR-ABL1* gene that are frequently responsible for TKI resistance (see p*age 29*). This information can help a doctor decide which drug to prescribe.

**TKI Adherence.** It is important for patients to take their TKIs as prescribed by their doctor. "Adherence" to an oral therapy means that a patient

- Takes the correct dose of medication
- Takes the medication at the correct time
- Never or rarely misses a dose
- Never takes an extra dose
- Does not take a dose with foods, liquids or other medications that are not allowed

In most patients, TKIs can control CML. Patients should not skip doses to try to reduce the side effects of the medication. Patients should tell their doctors about any side effects that they are experiencing. Doctors can provide supportive treatment (palliative care) to help patients manage these side effects.

Patients must take their medication as prescribed to achieve the best response. Poor adherence to the medication regimen is a primary reason for inadequate response to the prescribed treatment. Patients should not stop taking their medication, nor should they take less than the amount prescribed, unless they are instructed to do so by their doctors. Taking less than the amount prescribed can affect how well the medication works and may result in less than optimal treatment outcomes.

## Table 1. Some Drugs Approved and/or in Clinical Trials for the Treatment of CML

| Generic Name | Drug Class | Approved For |
|---|---|---|
| **Imatinib mesylate (Gleevec®)** | Tyrosine-kinase inhibitor (TKI) | 1. Newly diagnosed adults and children in chronic phase<br>2. Patients in chronic, accelerated or blast phase, after failure of interferon-alfa therapy |
| **Dasatinib (Sprycel®)** | TKI | 1. Newly diagnosed adults in chronic phase<br>2. Adults resistant to or intolerant of prior therapy in chronic, accelerated or blast phase<br>3. Pediatric patients age 1 year and older in chronic phase |
| **Nilotinib (Tasigna®)** | TKI | 1. Newly diagnosed adults in chronic phase<br>2. Adults resistant to intolerant of prior therapy in chronic or accelerated phase<br>3. Newly diagnosed pediatric patients age 1 year and older in chronic phase<br>4. Pediatric patients age 1 year and older in chronic phase who are resistant or intolerant of prior TKI therapy |
| **Bosutinib (Bosulif®)** | TKI | 1. Adults with chronic, accelerated or blast phase with resistance to or intolerance of prior therapy<br>2. Newly diagnosed adults in chronic phase |
| **Ponatinib (Iclusig®)** | TKI | 1. Adults for whom no other TKI is indicated<br>2. Adults with the T315I mutation |
| **Omacetaxine mepesuccinate (Synribo®)** | Protein synthesis inhibitor | Adults with chronic or accelerated phase who no longer respond to or have not been able to tolerate two or more TKIs |

The following drugs were used as initial therapy before TKIs were introduced. They may continue to be used in select patients.
**Interferon alfa (Roferon-A®, Intron A®)**
**Pegylated interferon alfa**
**Hydroxyurea (Hydrea®)**
**Cytarabine (Cytosar-U®)**
**Busulfan (Myleran®)**

New treatments may have been approved since this book was printed.
Check www.LLS.org/DrugUpdates or call (800) 955-4572.

**Chemotherapy.** Chemotherapy is generally used only in patients with blast phase CML to return the disease to the chronic phase. Very high-dose chemotherapy is sometimes used to prepare patients for an allogeneic stem cell transplant.

**Omacetaxine mepesuccinate (Synribo®),** a protein synthesis inhibitor, is a treatment option for adults with chronic or accelerated phase CML with resistance to and/or intolerance of two or more TKIs. Omacetaxine can be used to treat patients with all mutations (including the T315I mutation) that are resistant to TKIs. In general, its use is limited to patients who have exhausted all other TKI options and who are not candidates for an allogeneic transplant. Omacetaxine is given as a liquid injected under the skin. The most common side effects include

- Low red blood cell, white blood cell and platelet counts
- Diarrhea
- Nausea
- Fatigue
- Fever
- Infection
- Reaction at the injection site

**Immunotherapy.** Immunotherapy is a type of drug therapy that stimulates the immune system. Interferon is a substance naturally made by the immune system, but it can also be made in the laboratory. Interferon reduces the growth and division of cancer cells.

Prior to the introduction of TKIs, interferon was considered first-line treatment for patients who were not candidates for an allogeneic stem cell transplant. Currently, interferon therapy is less commonly used as a treatment for CML because, in general, TKIs are more effective and have fewer side effects. While interferon is no longer used as a first-line treatment for CML, it may be an option for patients who cannot tolerate the side effects of TKI therapy, or patients who are pregnant.

Interferon can cause significant side effects, including

- Trouble with concentration and memory
- Mood changes
- Flu-like symptoms, such as muscle aches, fatigue, fever, chills, headaches, nausea and vomiting
- Low red blood cell, white blood cell and platelet counts

These side effects continue as long as the patient uses the drug, but over time, they may become easier to tolerate. However, many patients, cannot cope with these side effects every day and need to discontinue treatment with interferon.

Recently, interferon has re-emerged as an option in CML treatment, with the advent of pegylated formulations. Pegylation is a chemical process designed to increase a drug's stability and retention time in the blood, while allowing for reduced dosing frequency. Pegylated interferon requires less frequent administration and is better tolerated by patients.

**Hematopoietic Stem Cell Transplantation (HSTC).** Transplantation is an option for some CML patients.

**Allogeneic Stem Cell Transplantation.** For certain patients with CML, allogeneic stem cell transplantation (infusion of donor stem cells into a patient) is the best-documented curative treatment at this time. However, this type of transplant can cause serious or even life-threatening complications and side effects. In addition, it is often not a good option for older patients or for patients who have other health problems. Results are very similar with the use of stem cells from matched siblings compared to use of cells from matched unrelated donors.

The decision to pursue allogeneic transplantation has become more complicated because many patients have very good responses to TKIs. Although transplantation has a proven curative track record for some CML patients, treatment with TKIs may be able to control the disease for very long periods and preserve quality of life without the serious side effects of transplantation.

A doctor will consider many important factors when deciding if an allogeneic transplant is the preferred choice of treatment for a patient. These factors include the patient's age, general health, the phase of CML, prior poor response to other treatments and the availability of a well-matched donor. Transplantation is considered for patients who have resistance to at least two types of TKIs, for patients whose CML is in accelerated or blast phase and for patients who are intolerant to all TKIs.

The most important prognostic factor for survival post-transplant is the patient's phase of CML. Approximately 80 percent of patients with chronic phase CML will be disease free for 5 years after transplant. In patients with accelerated phase CML, approximately 40 to 50 percent are disease free after 5 years, and only 10 to 20 percent of blast phase patients are alive and disease free after 5 years.

**Visit www.LLS.org/booklets to reach the free LLS booklet *Blood and Marrow Stem Cell Transplantation* for more information about all types of transplant.**

# Treating CML by Phase

Each phase of CML requires different treatment.

**Treatment for Chronic Phase CML.** TKI therapy is standard treatment for chronic phase CML. TKIs are often successful at managing CML for long periods of time. Four TKIs are approved as primary treatment for chronic phase CML:

- Imatinib
- Dasatinib
- Nilotinib
- Bosutinib

When choosing a first-line TKI, doctors may consider factors such as a patient's pre-existing health conditions, age and risk score, as well as the plus dose schedule and drug cost. After the start of therapy, doctors will monitor patients to evaluate treatment response. A patient who is responding well will stay on his or her current drug therapy. If the patient is not meeting treatment milestones, the doctor will need to find out why.

If the patient's current treatment is not working, a *BCR-ABL1* kinase domain mutation analysis (see *page 29*) should be done to check for mutations of the *BCR-ABL1* gene. The doctor will also determine whether the patient has been adhering to the treatment plan. There are a number of options at this point, which include:

- Advising patients who have not been taking their TKIs as prescribed about the importance of adhering to their medication regimen
- Increasing the dosage of the current drug (if possible)
- Switching to another TKI, for example, switching from imatinib to dasatinib, nilotinib, bosutinib or ponatinib
- Trying other therapies (such as omacetaxine, an option for patients with resistance or intolerance to two or more TKIs or interferon)
- Assessing whether an allogeneic stem cell transplant is an option

**Treatment for Accelerated Phase CML.** The goal in treating accelerated phase CML, just as with the chronic phase, is to eliminate all cells that contain the *BCR-ABL1* gene, leading to a remission. If this is not possible, the goal is to return the disease to the chronic phase. Treatment at a specialized center with doctors who have expertise in treating CML is recommended for patients in the accelerated phase of the disease.

In accelerated phase CML, the cancer cells often acquire new genetic mutations that may make treatments less effective. Patients should undergo *BCR-ABL1* gene

mutation analysis (see *page 29*) before starting treatment to determine which treatment option is best for them.

Treatment options for accelerated phase CML depend on the patient's previous treatments. If CML is diagnosed in the accelerated phase and the patient has not yet received a TKI, one treatment option is to begin TKI therapy. The drugs approved for TKI therapy include

- Imatinib
- Dasatinib
- Nilotinib
- Bosutinib

If the CML progresses from chronic phase to accelerated phase during TKI therapy, a doctor may increase the dosage of the current TKI (if possible) or prescribe another TKI that the patient has not received before. Other options include

- The TKI ponatinib, for patients who have not responded to two or more TKIs and for patients who have the T315I mutation
- The drug omacetaxine (an option only for patients who have experienced resistance to or intolerance of two or more TKIs)
- An allogeneic stem cell transplant

Another option for patients with accelerated phase CML is to receive treatment in a clinical trial. Clinical trials are studies done by doctors to test new drugs and treatments, or new uses for approved drugs and treatments. Clinical trials are one way for patients to obtain state-of-the-art cancer treatments. The goal of clinical trials for CML is to improve treatment and quality of life and to find a cure. Patients should talk to their doctors about the potential benefits and risks of participating in a clinical trial. See *Research and Clinical Trials* on *page 36*.

**Treatment for Blast Phase CML.** Patients with blast phase CML have leukemia cells that have become very abnormal. Blast phase disease acts more like acute leukemia, with higher blood counts and more severe symptoms. Treatment at a specialized center with doctors who have expertise in treating CML is recommended for patients in the blast phase of the disease.

Two important tests are needed before starting treatment for blast phase CML:

- The first test determines whether the blast phase involves myeloid or lymphoid blast cells. This test is important because the type of blast cells is a factor in the treatment decision.
- The second test, a *BCR-ABL1* kinase domain mutation analysis (see *page 29*), checks for mutations in the part of the *BCR-ABL1* gene that is targeted by TKIs.

Different mutations can make the BCR-ABL1 protein either more or less resistant to certain TKIs.

One option for patients with blast phase CML is to receive treatment within a clinical trial. Patients should talk to their doctors about the potential benefits and risks of participating in a clinical trials. See *Research and Clinical Trials* on *page 36*.

Another treatment option is for patients to receive TKI therapy, either with or without chemotherapy, and then proceed to an allogeneic stem cell transplant. In general the more potent second-generation TKIs are preferred for blast phase CML. Patients who respond to these drugs may still want to consider allogeneic stem cell transplantation. An allogeneic stem cell transplant is more likely to be successful if the disease can be returned to the chronic phase before transplantation.

# Measuring Treatment Response

After patients begin treatment, their doctors will periodically order blood and bone marrow tests to determine whether they are responding to treatment. A "treatment response" is an improvement related to the patient's treatment. Monitoring treatment response is one of the key strategies for managing CML. In general, the greater the response to drug therapy, the longer the disease will be controlled. **Table 2** on *page 30* shows the different types of treatment responses for CML.

There are three types of responses: hematologic, cytogenetic and molecular.

**Hematologic Response.** This response is described as either "partial" or "complete," depending on the results of a complete blood count (CBC) with differential. This test measures the number of red blood cells, white blood cells (including the different types of white blood cells) and platelets in the blood.

- Partial hematologic response—The numbers of each type of blood cell begin to return to a normal level.
- Complete hematologic response (CHR)—The blood counts have returned to normal. Most patients on TKI therapy will have a complete hematologic response within 1 month of beginning treatment.

**Cytogenetic Response.** This is a measurement of the number of cells in the bone marrow that contain the Ph chromosome (Ph+). Either cytogenetic analysis or a FISH test is used to measure this.

- Minor cytogenetic response—The Ph chromosome is found in more than 35 percent of cells in the bone marrow.
- Major cytogenetic response (MCyR)—There are 35 percent or fewer cells the Ph chromosome. This term is sometimes used to describe either a complete or partial cytogenetic response.

- Partial cytogenetic response (PCyR)—The Ph chromosome is found in 1 to 35 percent of bone marrow cells.
- Complete cytogenetic response (CCyR)—No cells with the Ph chromosome can be detected in the bone marrow.

Cytogentic analysis of bone marrow cells (bone marrow cytogenetics) is done at 3 month intervals to check the patient's response to therapy, if a reliable qPCR test is not available (see *Quantitative Polymerase Chain Reaction* on *page 9*).

**Molecular Response.** A molecular response is a decrease in the number of cells with the *BCR-ABL1* gene. A qPCR test measures the number of cells in the peripheral bloodstream that contain the *BCR-ABL1* gene. A patient's initial molecular response to treatment is significant in predicting outcome and in determining further treatment options.

- In an early molecular response, the *BCR-ABL1* level is 10 percent or less at 3 and 6 months after the start of treatment. This means that no more than 10 percent of cells—(10 out of every 100 cells)—have the *BCR-ABL1* gene.
- In a major molecular response (MMR), the *BCR-ABL1* level has decreased to 0.1 percent. This means that 1 out of every 1,000 cells has the *BCR-ABL1* gene. This is also referred to as a "3-log reduction."
- In a complete molecular response (CMR), no cells with the *BCR-ABL1* gene are found by qPCR. It is also referred to as a "deep molecular response."

**The International Scale (IS).** This is a standardized scale for measuring qPCR test results. The qPCR test measures the number of cells that have the *BCR-ABL1* gene. It is used to determine how well treatment is working. The International Scale defines the standard baseline as *BCR-ABL1* 100 percent. A log reduction indicates the *BCR-ABL1* level has decreased by a certain amount from the standard baseline.

- 1-log reduction indicates that the *BCR-ABL1* levels have decreased to 10 times below the standardized baseline. This means that 10 percent of cells (10 out of every 100 cells) have the *BCR-ABL1* gene. This is also written as "*BCR-ABL1* 10 percent." This reduction is equivalent to an early molecular response when achieved within 3 to 6 months of starting treatment.
- 2-log reduction means that *BCR-ABL1* levels have decreased to 100 times below the standardized baseline. This means that 1 percent of cells (1 out of every 100 cells) have the *BCR-ABL1* gene. This is also written as "*BCR-ABL1* 1 percent."
- 3-log reduction indicates that the *BCR-ABL1* levels have decreased to 1,000 times below the standardized baseline. This means that 0.1 percent of cells (1 out of every 1,000 cells) have the *BCR-ABL1* gene. This is written as "*BCR-ABL1* 0.1%." It is also known as a "major molecular response" (MMR).
- 4.5-log reduction is referred to as a "complete molecular response" (CMR) or a "deep molecular response." Doctors may refer to this as "MR4.5." A 4.5-log

reduction indicates that 0.0032% of cells (1 out of every 32,000 cells) have the *BCR-ABL1* gene. Achieving a deep molecular response is a sign of disease remission. Patients who achieve and then sustain a deep molecular response for a significant period of time may be considered candidates for discontinuing drug therapy under careful medical supervision. See *Treatment-Free Remission* on *page 32*.

Unfortunately, qPCR tests may not be standardized from laboratory to laboratory. Different laboratories may establish their own standardized baseline values. So, the same sample may produce slightly different results at different labs. Because of this, it is best to have samples sent to the same laboratory each time in order to receive consistent results. This will help patients and members of the healthcare team monitor treatment response more effectively.

For patients, qPCR testing is recommended every 3 months initially. After 2 years of achieving and maintaining a *BCR-ABL1* level of 1 percent or less, the test should be done every 3 to 6 months.

## *BCR-ABL1* Kinase Domain Mutation Analysis

Sometimes mutations occur in the part of the *BCR-ABL1* gene that alters the shape of the BCR-ABL1 protein. This can affect how TKIs bind to the BCR-ABL1 protein to block the growth signals.

A *BCR-ABL1* kinase domain mutation analysis is a test that looks for mutations in the *BCR-ABL1* gene that may cause certain TKIs to stop working. A *BCR-ABL1* gene mutation analysis should be performed if there is

- An inadequate response to initial TKI therapy
- A failure to meet a treatment milestone
- A loss of hematologic response, loss of cytogenetic response, 1-log increase in *BCR-ABL1* levels or a loss of major molecular response in the context of continuous therapy
- Progression to accelerated phase or blast phase CML

Mutation testing does not need to be done in patients who are switching medication because of side effects.

Among the *BCR-ABL1* mutations:

- T315I is resistant to imatinib, dasatinib, nilotinib and bosutinib
- F317L and V299L are resistant to dasatinib
- Y253H, E255K/V and F359C/V are resistant to nilotinib
- T315I, G250E and V299L are resistant to bosutinib

E255K/V, F359C/V and T315I are the mutations most commonly associated with disease progression and relapse.

## Table 2. Chronic Myeloid Leukemia Treatment Responses

| Type of Response | | Features | Test Used to Measure Response |
|---|---|---|---|
| **Hematologic** | Complete hematologic response (CHR) | • Blood counts completely return to normal<br>• No blasts in the peripheral blood<br>• No signs or symptoms of disease; spleen returns to normal size | Complete blood count (CBC) with differential |
| **Cytogenetic** | Complete cytogenetic response (CCyR) | No Philadelphia (Ph) chromosome detected | Bone marrow cytogenetics or FISH |
| | Partial cytogenetic response (PCyR) | 1% to 35% of cells have the Ph chromosome | |
| | Major cytogenetic response (MCyR) | 35% or fewer cells have the Ph chromosome | |
| | Minor cytogenetic response | More than 35% of cells have the Ph chromosome | |
| **Molecular** | Complete molecular response (CMR) | No *BCR-ABL1* gene detectable | Quantitative PCR (qPCR) using International Scale (IS) |
| | Major molecular response (MMR) | At least a 3-log reduction* in *BCR-ABL1* levels or *BCR-ABL1* 0.1% | |

* A 3-log reduction is a 1/1,000 or 1,000-fold reduction of the level of cells with the *BCR-ABL1* gene.

Table 2. Treatment responses for CML. Source: NCCN Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia, version 1.2019.

For people who experience a loss of response to a TKI, or those who do not achieve the expected response within a given period of time (see **Table 3** on *page 31*), the most common options are switching to another approved TKI or participating in a clinical trial.

## Table 3. Treatment Response Milestones and Follow-up Recommendation Guidelines

| | TIME AFTER START OF TREATMENT | | | |
|---|---|---|---|---|
| ***BCR-ABL1* (IS)** | **3 months** | **6 months** | **12 months*** | **More than 15 months** |
| > 10% | YELLOW | RED | | |
| > 1% – 10% | GREEN | | YELLOW | RED |
| ≤ 1% | GREEN | | | |

| Color Code | Concern | Treatment Team Considerations | Potential Decisions About Treatment |
|---|---|---|---|
| RED | TKI-resistant disease | • Evaluate patient compliance and drug interactions<br>• Consider *BCR-ABL1* gene mutation testing | • Switch to alternate TKI<br>• Evaluate for allogeneic stem cell transplantation |
| YELLOW | Possible TKI resistance | • Evaluate patient compliance and drug interactions<br>• Consider *BCR-ABL1* gene mutation testing<br>• Consider bone marrow cytogenetic testing to assess for MCyR at 3 months or CCyR at 12 months | • Switch to alternate TKI<br>***OR***<br>• Continue same TKI (other than imatinib)<br>***OR***<br>• Dose escalation of imatinib (to a max of 800 mg)<br>***AND***<br>• Consider evaluation for allogeneic stem cell transplantation |
| GREEN | No concerns – treatment is working | • Monitor response<br>• Monitor and manage side effects as needed | • Continue same TKI† |

Table 3. Adapted from NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia; version 1.2019.
Abbreviations: McYR, major cytogenic response; CCyR; complete cytogenic response; TKI, tyrosine kinase inhibitor.
**BCR-ABL1* 0.1% at 12 months is associated with a very low probability of disease progression and a high likelihood of achieving a subsequent MR4.5, which may allow for discontinuation of TKI therapy.
†Discontinuation of TKI with careful monitoring is possible in selected patients.

Every patient responds differently to CML drug therapy. These general guidelines for CML drug therapy are available online from the National Comprehensive Cancer Network (NCCN) and the European Leukemia Net (ELN). (See the section entitled *More Information* on *page 56* for links to these and other resources.)

An individual's CML drug therapy response is measured against his or her own results at the start of therapy (the start of therapy is called "baseline"). A complete molecular response is optimal, but only some patients attain this. Even without a complete molecular response, CML may be well controlled by drug therapy.

# Treatment-Free Remission

Because of advances in the understanding of CML, as well as the very successful treatment of patients with TKIs, treatment-free remission (TFR) is now an emerging treatment goal. Many patients with CML have achieved a deep and stable response to treatment. Treatment-free remission is achieved when a patient who has discontinued TKI therapy maintains a deep molecular response (DMR, also known as complete molecular response or CMR) and does not need to restart treatment.

The feasibility and safety of discontinuing TKI therapy has been evaluated in several studies. Patients in the chronic phase of CML who have maintained a stable and deep molecular response (DMR) for at least two years are considered good candidates for TKI therapy discontinuation under careful medical supervision.

In 2017, the FDA expanded the nilotinib product label to include the safe discontinuation of this medication for two patient groups:

- Adult patients with newly diagnosed CML in chronic phase who were treated with nilotinib for 3 or more years and who have achieved DMR for at least 2 years
- Adult chronic-phase CML patients who received frontline treatment with imatinib and who switched to nilotinib due to resistance to or intolerance of imatinib, and who received nilotinib for 3 or more years and have achieved DMR for at least 1 year

**Table 4,** *below,* lists the main clinical criteria for patients who want to attempt to discontinue TKI therapy and achieve treatment-free remission.

### Table 4. Patient Clinical Criteria for TKI Discontinuation

| Parameter | Criteria |
|---|---|
| Age | 18 years and older |
| CML phase | Chronic phase only |
| BCR-ABL1 transcripts | e13a2, e14a2, or e13a2 + e14A2 |
| TKI treatment duration | At least 3 years |
| Molecular response | MR4.5 |
| DMR duration | At least 2 years |
| Prior treatment history | No disease progression, resistance or suboptimal response |

Table 4 shows the clinical criteria for TKI therapy discontinuation.
Abbreviations: DMR, deep molecular response; MR4.5, molecular response of 4.5-log reduction on the International Scale, indicating complete molecular response; TKI, tyrosine kinase inhibitor.

CML patients have many reasons to attempt treatment-free remission. Motivations may include convenience, economic savings and quality-of-life factors. After discontinuing TKI therapy, some patients might experience musculoskeletal pain. This is known as TKI withdrawal syndrome. Generally, the pain can be managed with over-the-counter pain medication. Although this syndrome can last for months, it can often be controlled with nonprescription drugs or nonsteroidal anti-inflammatory drugs (NSAIDs), and in more severe cases, with corticosteroids. CML patients may be reluctant to try treatment-free remission due to fear of relapse or disease progression. In the case of relapse, nearly all patients who need to restart therapy are able to obtain and maintain a major molecular response again. Treatment-free remission periods may last from a few months to many years.

Patients should discuss with their treatment team whether attempting treatment-free remission may be a potential option in their case. Consultation with an experienced CML doctor is essential.

**For more information on this topic, please see the free LLS publication *Treatment-Free Remission for Chronic Myeloid Leukemia Patients*.**

# Children and Young Adults with CML

A small percentage of patients diagnosed with CML are children and young adults. From 2011 to 2015, the most recent 5-year period for which data are available, CML accounted for about 3.1 percent of new cases of leukemia in children, adolescents and young adults younger than age 20.

The treatment of children with CML is not standardized. It often follows guidelines developed for adults, even though there are differences between CML in children and adults in terms of disease presentation and progression. Some studies indicate that children and young adult patients have lower rates of complete cytogenetic and major molecular responses compared with older adults. Children and young adults might have a slightly higher risk of transformation to accelerated and blast phase. Children with CML should be treated by pediatric hematologist-oncologists (doctors who specialize in treating pediatric patients with blood cancer).

Although there are not a great number of studies focused on the treatment of pediatric patients with CML, there is evidence that imatinib may slow growth, particularly in children who are treated before they reach puberty. Other rare side effects of imatinib seen in adults, such as cardiotoxicity and thyroid dysfunction, appear to be very rare in children.

The following medications are used in the treatment of children with CML.

- **Imatinib (Gleevec®)** is approved to treat newly diagnosed pediatric patients with Philadelphia chromosome positive CML (Ph+ CML) in chronic phase.
- **Dasatinib (Sprycel®)** is approved to treat pediatric patients age 1 year and older with Ph+ CML in chronic phase.
- **Nilotinib (Tasigna®)** is approved for pediatric patients age 1 year and older with
  - Newly diagnosed CML in chronic phase
  - Chronic-phase CML in children resistant to or intolerant of prior TKI therapy.

Because children with CML may receive TKI therapy for much longer than adults and during periods of active growth, follow-up care is very important. In addition to evaluating responses to therapy, doctors should also monitor the following in their pediatric patients:

- Height and weight—Doctors should consider a bone scan and a bone density scan if there is evidence of abnormal growth.
- Puberty—Doctors should refer patients to an endocrinologist if there is a delay in puberty.
- Thyroid function
- Heart—Patients should have an annual echocardiogram.

Poor adherence to therapy, particularly in adolescents and young adults, is an additional concern. With oral TKIs, it is essential to follow the doctor's directions and keep taking the medication for as long as prescribed. Nonadherence to TKI treatment (meaning the patient does not take the medication as scheduled) is known to increase the risk of lower response or possibly treatment failure.

Taking into account the potential concerns of lifelong TKI treatment, researchers are studying TKI discontinuation after a period of complete molecular response. Treatment-free remission is now considered a goal of treatment for selected patients and is a focus of study in various ongoing clinical trials (see *page 36*). Intermittent TKI dosing is another potential method to reduce long-term side effects in pediatric CML patients, but more studies are needed to evaluate this approach. Allogeneic stem cell transplantation is an additional treatment option, but it is generally used in cases of relapse or accelerated/blast phase CML. Because there have been no randomized controlled trials comparing stem cell transplantation with imatinib use in children, due to the small number of pediatric patients, the decision on how to treat CML has been individualized. Stem cell transplantation should be evaluated against the complications associated with lifelong TKI use.

Talk to your child's doctor about the best treatment option for your child and any concerns regarding the risks associated with your child's therapy. It is important for your child to be seen by a doctor who specializes in pediatric leukemia.

**Visit www.LLS.org/booklets to reach the free LLS booklets *Choosing a Blood Cancer Specialist or Treatment Center Facts* and *Coping with Childhood Leukemia and Lymphoma.***

## Fertility, Pregnancy and TKIs

Patients who are of childbearing age, as well as the parents of children with cancer, should ask their healthcare team to explain how treatment may affect the ability to have children. Patients with CML who will be taking TKIs should discuss fertility preservation with their doctor before starting TKI therapy.

Growing numbers of CML patients of childbearing age are living with stable remissions and are considering having children while taking TKIs. In some men who take TKIs, researchers have observed low sperm counts and poor sperm motility decreased (ability for sperm to move). Male patients should consider having a fertility evaluation before trying to conceive a baby. Prior to treatment, men may want to consider cryopreservation (sperm banking). Depending on the TKI, their doctor may recommend discontinuing treatment 3 to 4 weeks prior to a planned conception. Men taking imatinib at the time of conception are not at risk of passing on the Ph chromosome abnormalities of CML to their children. Most medical experience to date suggests there is little risk associated with fathering children while on TKI therapy.

For female patients who want to become pregnant, however, the issues are more complex and there is limited data. Imatinib, dasatinib and nilotinib are known to cause embryonic or fetal toxicities in animal studies. In some instances, female patients receiving TKI therapy at the time of conception have had miscarriages or babies born with congenital abnormalities.

A patient should consult with her hematologist-oncologist, as well as a high-risk obstetrician, to discuss the potential risks of discontinuing TKI therapy during pregnancy, versus the potential risks to the fetus of continuing TKI therapy. Doctors may advise planning the pregnancy when the patient's response to therapy is as deep as possible, at least a major molecular response. The patient would stop therapy prior to conception and during the pregnancy. The patient would then resume TKI therapy immediately after the birth of her child and refrain from breastfeeding. During pregnancy the patient should be closely monitored through blood tests for signs of disease progression. This option should only be done under the close observation of a hematologist-oncologist and an obstetrician who specializes in high-risk pregnancies.

At present, there are no data to suggest that either imatinib or any other TKI drug can be taken safely during pregnancy. Current recommendations include counseling so that potential parents understand the

- Risk of relapse for mothers who discontinue therapy during pregnancy
- Risk of congenital abnormalities for babies exposed to TKIs during pregnancy
- Need for women on TKI therapy to refrain from breastfeeding their babies
- Treatment options, both during and after pregnancy

Treatment-free remission is now an emerging treatment goal for many patients with CML who have achieved a deep and stable response to treatment for at least two years. The medication nilotinib has been approved for safe discontinuation in a select group of patients who meet specific criteria. Female patients who are interested in having children should discuss all their options with their treatment team, including the possibility of achieving treatment-free remission. See *page 32* for more information on this topic.

## Research and Clinical Trials

Every new drug or treatment regimen goes through a series of studies called "clinical trials" before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians, researchers and patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option. Patient participation in past clinical trials has resulted in the therapies we have today.

People with CML are encouraged to explore treatment options in clinical trials. Many clinical trials that test new drugs and treatments are supported by LLS research programs. New drugs and therapies are tested in clinical trials before they are approved by the FDA as standard treatments.

There are clinical trials for newly diagnosed patients, for patients with advanced disease and for patients who are either resistant or intolerant to their current medications. Clinical trials hold promise to further improve treatment outcomes in CML patients.

LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, 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.

**Research Approaches.** The following approaches are under study in clinical trials for the treatment of patients with CML.

**Improving Current Treatments.** Based on the positive results of tyrosine kinase inhibitor (TKI) therapy in chronic phase CML, many trials are looking at ways to further optimize the use of these drugs. This research includes

- Determining which TKI should be used as initial therapy for different patients with chronic phase CML
- Establishing the best time to switch patients to second-line therapy
- Finding out whether deeper responses are achieved when other agents are added to TKIs
- Preventing and/or predicting long-term side effects of TKIs
- Determining which patients can successfully discontinue TKI therapy

### New Drug Therapies and Drug Combinations

- **Asciminib (ABL001)** is an investigational tyrosine kinase inhibitor (TKI) that binds to the ABL1 portion of the BCR-ABL1 fusion protein at a location that is distinct from the ATP-binding domain. This medication is currently under study in clinical trials in combination with other TKIs, such as imatinib and dasatinib.
- **Ruxolitinib (Jakafi®)** is a pan-Janus kinase inhibitor that is already approved to treat patients who have been diagnosed with myelofibrosis or polycythemia vera. This drug is being studied in clinical trials in combination with TKIs.
- **Ipilimumab (Yervoy®)** is a monoclonal antibody and also an immune checkpoint inhibitor that is currently being evaluated, in combination with dasatinib, in patients with chronic or accelerated phase CML.
- **Tyrosine kinase inhibitor in combination with pioglitazone.** Pioglitazone is a drug used to treat type 2 diabetes. In early studies, it has shown the ability to induce cell death in leukemic cells when combined with a TKI.
- **Tyrosine kinase inhibitor in combination with interferon alpha.** Several studies have shown improved molecular response rates when using this combination, compared with imatinib alone.

**TKI Discontinuation Studies.** Treatment of CML with TKIs has advanced to a point where many patients are able to achieve deep and durable remissions. The feasibility and safety of discontinuing TKI therapy, along with close monitoring of carefully selected patients who have achieved and maintained a deep molecular response (DMR) for at least two years, continues to be evaluated in several long-term studies. (TKI discontinuation can also occur outside of a clinical trial, under certain circumstances.) For more information on treatment-free remission, see *page 32*.

**WT1 Peptide Vaccine.** The Wilms Tumor 1 (WT1) protein is expressed in CML, acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) cells, making this protein a good target for immunotherapy. A WT1 peptide vaccine is currently under study in clinical trials for CML to test whether the vaccine can increase the number of immune cells responding to the cancer and thereby slow progression of the disease. See the free LLS booklet *Immunotherapy Facts* for information about the development of blood cancer vaccines.

**Visit www.LLS.org/booklets to see the free LLS booklet *Immunotherapy Facts*.**

**Reduced-Intensity Stem Cell Transplantation.** A modified form of allogeneic transplantation known as "reduced-intensity" or "nonmyeloablative" allogeneic stem cell transplantation may be an option for CML patients who do not respond to other treatments. Patients being prepared for a reduced-intensity transplant receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant, compared to the doses given to patients receiving a traditional allogeneic transplant. The theory being tested with a reduced-intensity transplant is that by undergoing less toxic procedures prior to the transplant, the body is better able to withstand the transplant. However, full donor engraftment would ideally still take place, and the desired graft-versus-leukemia effect would still occur. Ongoing clinical trials are evaluating the use of this type of transplantation in adult and pediatric patients.

**Visit www.LLS.org/booklets to see the free LLS booklet *Blood and Marrow Stem Cell Transplantation.***

# Follow-up Care

CML follow-up care varies from patient to patient. CML patients

- Will need to see their doctor on a regular basis. The doctor will evaluate their health, check blood cell counts and their molecular responses to treatment using qPCR tests, and possibly perform bone marrow tests.
- Are advised to receive certain vaccinations, including vaccinations for influenza and pneumococcal pneumonia. There are two types of pneumococcal vaccines available for adults: a pneumococcal polysaccharide vaccine (PPSV23) and a pneumococcal conjugate vaccine (PCV13). Immunizations using live organisms or with high viral loads, such as the herpes zoster or the Zostavax® vaccine (the live shingles vaccine), should not be administered. CML patients can receive the shingles vaccine Shingrix®, because it is an "inactivated" rather than a "live" vaccine. Your doctor can give you more information.
- Always need to keep good records and treatment notes. This information should include
  - Doctors' names and contact information
  - Medical history
  - CML diagnosis
  - Copies of all pathology reports
  - A list of all treatments
  - Names of drugs
  - Transplant information
  - Any other important information

# Incidence, Causes and Risk Factors

**Incidence.** CML is a relatively rare disease. From 2011-2015 the incidence of CML was 1.8 per 100,000 men and women (see **Figure 4**, *below*). CML is slightly more common in men than it is in women, and most cases of CML occur in adults. According to the National Cancer Institute, CML is most frequently diagnosed in people between the ages of 80 and 84. The median age at diagnosis is 65 years. A small number of children develop CML (See the section *Children and Young Adults with CML* on *page 33*).

## Figure 4. Chronic Myeloid Leukemia (CML): Age-Specific Incidence Rates 2011-2015

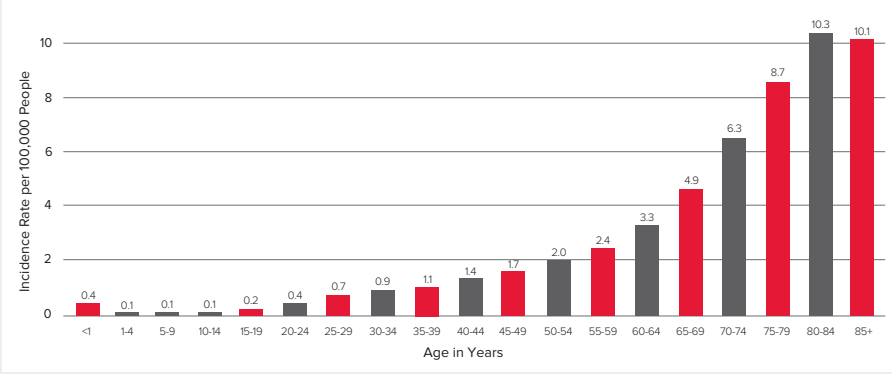


Figure 4. The horizontal axis shows five-year age intervals. The vertical axis shows the frequency of new cases of CML per 100,000 people, by age-group.
Source: Surveillance, Epidemiology and End Results (SEER) Program; National Cancer Institute; 2018.

**Causes.** No one is born with CML. It is not passed from parent to child. It occurs when there is an injury to the DNA of a single bone marrow cell. The mutated cell multiplies uncontrollably and crowds out the healthy red blood cells, white blood cells and platelets in the bone marrow. The CML cells then overflow into the bloodstream. Because CML is a slow growing form of leukemia, it does not completely interfere with the development of mature red blood cells, white blood cells and platelets. As a result, CML is generally less severe than acute forms of leukemia and often patients do not have any symptoms when they are diagnosed with CML.

**Risk Factors.** A risk factor is anything that increases a person's chance of developing a disease. The following are risk factors for CML:

- Gender—CML is slightly more common in males than females.
- Age—The risk of developing CML increases with age.

- Radiation exposure—In a small number of patients, CML is caused by exposure to very high doses of radiation (such as being a survivor of an atomic bomb blast or a nuclear reactor accident).
  - A slight increase in risk also occurs in some individuals treated with high-dose radiation therapy for other cancers, such as lymphoma. But most people treated for cancer with radiation do not develop CML, and most people who have CML have not been exposed to high doses of radiation.
  - Exposures to diagnostic dental or medical x-rays have not been associated with an increased risk of CML.

**Feedback.** Visit www.LLS.org/publicationfeedback to give suggestions about this booklet.

# Normal Blood and Bone Marrow

**Blood.** Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients to the lungs and tissue. It carries away waste products, taking them to the kidneys and liver, which clean the blood. Blood is composed of plasma and cells.

**Plasma.** The plasma inside the blood is mostly made up of water in which the blood cells are suspended. Plasma contains many dissolved chemicals, each of which has a special role. They include

- Proteins
  - Albumin, the most common blood protein
  - Blood-clotting proteins made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
  - Immunoglobulins, proteins that help the body fight infection
- Hormones, such as thyroid hormone and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B12
- Electrolytes, such as calcium, potassium and sodium

**Blood Cells.** The blood cells are suspended in the plasma.

There are three types of blood cells. They are

- Red blood cells that carry oxygen and
  - Make up a little less than half of the body's total blood volume

- Are filled with hemoglobin, a red protein that picks up oxygen from the lungs and delivers it to the cells throughout the body. Hemoglobin then picks up carbon dioxide from the cells and delivers it back to the lungs, where it is removed when a person exhales.

- Platelets
  - These are small cells (one-tenth the size of red blood cells).
  - They help stop bleeding from an injury. For example, when a person has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the blood vessel, clump together and plug up the bleeding site with the help of blood-clotting proteins (such as fibrin) and electrolytes (such as calcium).
- White blood cells (WBCs) that fight infections. There are several types of WBCs, including
  - Neutrophils and monocytes. These are cells called "phagocytes" that eat and kill bacteria and fungi. Unlike the red blood cells and platelets, monocytes can leave the bloodstream and enter the tissue, where they can attack invading organisms and fight off infection.
  - Eosinophils and basophils. These white blood cells respond to allergens and parasites.
  - Lymphocytes. This type of white blood cell is mostly found in the lymph nodes, spleen and lymphatic channels. Lymphocytes are a key part of the immune system. There are three major types of lymphocytes:
    - T lymphocytes (T cells)
    - B lymphocytes (B cells)
    - Natural killer (NK) cells

**Figure 5. Blood Cell & Lymphocyte Development**

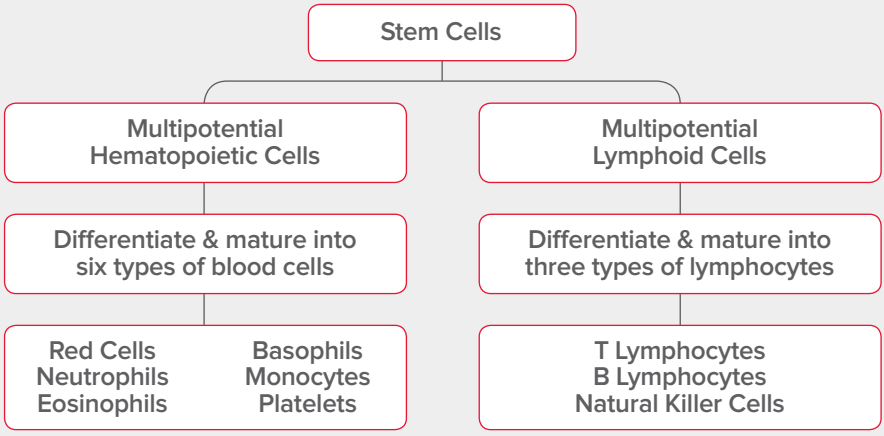


Figure 5. Stem cells develop into blood cells and lymphoid cells.

Marrow is a spongy tissue where blood cell development takes place. It occupies the central cavity of bones. In newborns, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have functioning marrow. In adults, the spine (vertebrae), hip and shoulder bones, ribs, sternum, pelvis and skull contain the marrow that continues to make blood cells. The process of blood cell formation is called "hematopoiesis." A small group of cells, the stem cells, develop into all the blood cells in the marrow by the process of differentiation (see **Figure 5** on *page 42*).

In healthy individuals, there are enough stem cells to keep producing new blood cells continuously. Blood passes through the marrow, where it picks up the fully developed and functional red and white cells and platelets that will circulate in the bloodstream.

Some stem cells also enter the blood and circulate. They are present in such small numbers that they cannot be counted or identified by standard blood count tests. Their presence in the blood is important because they can be collected by a special technique for stem cell donation. There are also methods to induce more stem cells to leave the marrow and circulate in the blood, allowing a greater number of stem cells to be collected for donation. If enough stem cells are harvested from a compatible donor, they can be transplanted into a recipient.

Stem cell circulation, from marrow to blood and back, also occurs in the fetus. After birth, placental and umbilical cord blood can be collected, stored and used as a source of stem cells for transplantation.

# Resources and Information

LLS offers free information and services to patients and families affected by blood cancer. This section of the booklet lists various resources that can be helpful to you. Use this information to learn more, to ask questions and to make the most of your healthcare team members' knowledge and skills.

## For Help and Information

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

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

**Clinical Trials Support Center.** Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, 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.

**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.

**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.

**Financial Assistance.** LLS offers financial assistance to individuals who have blood cancer. Please visit www.LLS.org/finances for more information.

***Co-Pay Assistance Program.*** LLS offers insurance premium and medication co-pay assistance for certain eligible patients. For more information, please

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

**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 consult or 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.

**Suggested Reading.** LLS provides a list of selected books recommended for patients, caregivers, children and teens. Please visit www.LLS.org/SuggestedReading to find out more.

## Community Resources and Networking

**LLS Community.** The one-stop virtual meeting place for talking with other patients and keeping up to date with the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Please 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.

**LLS Chapters.** LLS offers community 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 the nearest 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. For more information, please visit www.LLS.org/ResourceDirectory to obtain our directory.

**Advocacy.** The LLS Office of Public Policy (OPP) enlists volunteers to advocate for policies and laws to speed the approval of new treatments and improve access to quality medical care. For more information, please

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

## Additional Help for Specific Populations

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

**Language Services.** Let members of your healthcare team know if you need a language interpreter or other assistance, such as a sign language interpreter. Often, these services are free.

**Children's Concerns.** CML occurs in a small number of children. A family that has a child diagnosed with CML is thrown into an unfamiliar world of treatment and follow-up care. The child, parents and siblings will all need support. Help is available. Do not hesitate to ask for assistance for your child, yourself or other family members, even if you are already working with a psychologist, social worker or child-life specialist.

For practical guidance on how to support your child and other family members, deal with your own concerns, inform extended family and friends and make the transition to life after treatment ends, please

- See the free LLS booklet *Coping with Childhood Leukemia and Lymphoma*
- Call: (800) 955-4572 to ask about *The Trish Greene Back to School Program for Children with Cancer*

**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 visit www.publichealth.va.gov/exposures/agentorange or call the Department of Veterans Affairs at (877) 222-8387.

**World Trade Center Survivors.** People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get 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. Enter “depression” in the search box

# Health Terms

***ABL1* Gene.** A gene from chromosome 9 that breaks off and migrates to chromosome 22. The *ABL1* gene joins the *BCR* gene on chromosome 22 to form the *BCR-ABL1* fusion gene. The *BCR-ABL1* fusion gene is found in most patients with CML and in some patients with acute lymphoblastic leukemia. The gene symbol "*ABL1*" is derived from the name of the scientist Herbert Abelson, who discovered the gene while studying cancer-causing viruses in mice.

**Allogeneic Stem Cell Transplantation.** A treatment that uses healthy donor stem cells to restore a patient's damaged or diseased cells in the bone marrow. See the free LLS publication, *Blood and Marrow Stem Cell Transplantation*.

**Anemia.** A health condition in which the number of red blood cells is below normal. This results in a diminished ability of the blood to carry oxygen. Severe anemia can cause a pale complexion, weakness, fatigue and shortness of breath. See Hematocrit.

**Apheresis.** A process using a machine to take out the needed parts of the donor's blood and then to return the unneeded parts back to the donor. This process allows certain parts of blood, including red blood cells, white blood cells and platelets, to be removed separately and in large volumes.

**Basophil.** A type of white blood cell that has granules (small particles) with enzymes that are released during allergic reactions.

***BCR-ABL1.*** The fusion gene that causes CML. See Tyrosine Kinase.

**Blast Cell.** An immature (young) blood cell.

**Bone Marrow.** A spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried in the bloodstream throughout the body.

**Bone Marrow Aspiration.** A test that examines bone marrow cells to detect cell abnormalities. A liquid bone marrow sample is usually taken from the patient's hip bone using a special needle. Normally this test is done at the same time as a bone marrow biopsy.

**Bone Marrow Biopsy.** A test to examine bone marrow cells to detect cell abnormalities. After medication is given to numb the skin, a special hollow biopsy needle is used to remove a sample of bone containing marrow, usually from the hip (pelvic) bone. Bone marrow aspiration and bone marrow biopsy may be done in either the doctor's office or in a hospital. The two tests are almost always done together.

**Bone Marrow Transplantation.** See *Allogeneic Stem Cell Transplantation*.

**Chemotherapy.** Treatment that stops the growth of cancer cells, either by killing the cancer cells or by preventing them from dividing.

**Chromosomes.** Threadlike structures within cells that carry genes in a linear order. Human cells have 23 pairs of chromosomes.

**Cord Blood Stem Cells.** Stem cells collected from the placenta and umbilical cord after a baby is born. These stem cells can repopulate the bone marrow and produce blood cells in patients undergoing stem cell transplantations.

**Cytogenetic Analysis.** The process of analyzing the number and size of the chromosomes in cells. It detects chromosome alterations and, in some cases, may identify the actual genes that have been affected. These findings help healthcare professionals diagnose specific types of blood cancers, determine treatment approaches and monitor a patient's response to treatment. The individual who prepares and examines the chromosomes and interprets the results is called a cytogeneticist.

**Differentiation.** The process that occurs when stem cells develop and mature and take on a new function. Stem cells mature into red blood cells, platelets or white blood cells. See Hematopoiesis.

**Donor Lymphocyte Infusion (DLI).** A therapy often used for patients after an allogeneic bone marrow transplant. In this infusion procedure, patients are given lymphocytes (white blood cells) that come from the original transplant donor to help attack remaining cancer cells.

**Drug Intolerance.** Inability to tolerate the side effects of a drug.

**Drug Resistance.** The failure of cancer cells, viruses or bacteria to respond to a drug used to kill or weaken them.

**Eosinophil.** A type of white blood cell that promotes inflammation during allergic reactions and helps fight certain parasitic infections.

**European Treatment Outcome Study (EUTOS) score.** A scoring system that estimates survival of patients who have CML. Patients are classified as "high risk" or "low risk" on the basis of the percentage of basophils in their peripheral blood and the size of their spleen.

**Fluorescence In Situ Hybridization (FISH).** A technique for studying abnormal chromosomes in cells and tissues. Pieces of DNA that contain fluorescent molecules are added to cells or tissues on a slide. When the pieces of DNA bind to specific genes or chromosomes, they light up when viewed under a microscope.

**Graft-Versus-Tumor Effect (Graft-Versus-Leukemia Effect).** Transplanted blood stem cells (the graft) perceive the leukemia cells in a transplant patient's body as foreign and attack the cancer cells, as they are intended to do.

**Granulocyte.** A type of white blood cell with many particles (granules) in the cell body. Neutrophils, eosinophils and basophils are types of granulocytes.

**Hasford Scoring System.** A scoring system that estimates survival of patients with CML. The system designates patients as "low risk," "intermediate risk" or "high risk."

Hasford scores are based on the following diagnostic markers:

- The size of the spleen
- The blood platelet count
- The patient's age
- The percentage of blast cells circulating in the peripheral blood
- The number of eosinophils and basophils circulating in the peripheral blood

**Hematocrit.** The percentage of whole blood that is made up of red blood cells. The normal range for men is 40 to 54 percent and 35 to 47 percent for women. Anemia occurs when the hematocrit level is below normal.

**Hematologic.** Of, or relating to, blood.

**Hematologist.** A doctor who specializes in blood cell diseases.

**Hematopathologist.** A doctor who has special training in identifying diseases of the blood cells by examining blood, bone marrow and lymph, as well as other tissues, under a microscope.

**Hematopoiesis.** The formation and development of blood cells in the bone marrow. For the blood cell development process, see *Normal Blood and Bone Marrow* on *page 41*.

**Hyperleukocytosis.** A very high white blood cell count, often found in people when they are diagnosed with leukemia and most often in patients with chronic myeloid leukemia.

**Immunotherapy.** A treatment that uses the body's immune system to treat cancer and other diseases.

**Leukocyte.** Also known as "white blood cell." A type of blood cell that is part of the body's immune system. It defends the body against infections and other diseases. Types of leukocytes include granulocytes (neutrophils, eosinophils and basophils), monocytes and lymphocytes (T cells and B cells). See White Blood Cell.

**Lymph Node.** A bean-sized structure that is part of the body's immune system. Throughout the body, there are hundreds of lymph nodes that contain lymphocytes (white blood cells) that help fight infection and disease.

**Lymphocyte.** A type of white blood cell that performs an essential role in the body's immune system. There are three major types of lymphocytes. They are

- B lymphocytes that produce antibodies to fight infections
- T lymphocytes that help protect the body from infections and may help the body fight cancer
- Natural killer (NK) cells that attack virus-infected cells or tumor cells

**Macrophage.** Called a "scavenger cell," a macrophage is a type of white blood cell that surrounds and kills microorganisms, removes dead cells and stimulates the action of other immune system cells. See Monocyte.

**Minimal Residual Disease (MRD).** The small number of cancer cells that may remain after treatment and cannot be detected in the blood or bone marrow by using standard tests, such as examining cells under the microscope. These cells, however, can be detected with more sensitive molecular tests, such as quantitative polymerase chain reaction (qPCR).

**Monocyte.** A type of white blood cell that is made in the bone marrow and travels through the blood to tissues in the body where it becomes a macrophage. See Macrophage.

**Mutation.** A change in the DNA of a cell. A mutation may be caused by an error in cell division, or it may be caused by contact with DNA-damaging substances in the environment.

**Myelocyte.** A bone marrow cell that is a precursor of a mature granulocyte found in the blood. Myelocytes are not present in the blood of healthy individuals.

**Neutrophil.** A type of white blood cell and principal phagocyte (microbe-eating cell) in the blood. It is the main type of cell that combats infection. Patients with certain blood cancers and cancer patients who have received treatment such as chemotherapy often have low neutrophil counts, which makes them very susceptible to infections.

**Nonmyeloablative Allogeneic Stem Cell Transplantation.** See Reduced-Intensity Stem Cell Transplantation.

**Oncogene.** A changed (mutated) gene that contributes to the development of cancer. Several subtypes of acute myeloid leukemia, acute lymphoblastic leukemia and lymphoma, and nearly all cases of chronic myeloid leukemia, are associated with an oncogene. See Mutation.

**Oncologist.** A doctor who has special training in diagnosing and treating cancer.

**Palliative Therapy.** Specialized medical care given to relieve the symptoms and reduce the suffering caused by cancer and other serious illnesses.

**Pathologist.** A doctor who detects and identifies disease by examining body tissue and fluids under a microscope.

**Peripheral Blood.** The blood that circulates throughout the body in the arteries, capillaries and veins.

**Phagocyte.** A type of white blood cell that protects the body from infection by eating and killing micro-organisms, such as bacteria and fungi. The two main types of phagocytes are neutrophils and monocytes. Once an infection occurs, phagocytes migrate from the bloodstream and enter the infected tissue. Chemotherapy and radiation can decrease the numbers of these cells, so patients are more likely to get an infection.

**Philadelphia Chromosome (Ph Chromosome).** An abnormality of chromosome 22 found in the bone marrow and blood cells of most patients with chronic myeloid leukemia and of some patients with acute lymphoblastic leukemia. It is formed when parts of chromosome 9 and 22

break off and trade places. The result is a chromosome 22 that is shorter than normal. The exchange of DNA between chromosomes 9 and 22 results in the creation of a new gene (an oncogene) called *BCR-ABL1* on chromosome 22.

**Platelet.** A small, colorless blood cell that helps control bleeding. Platelets travel to and then collect at the site of a wound. The platelets' sticky surface helps them to form clots at the site of the wound and stop bleeding. Platelets make up about one tenth of the volume of red blood cells. Also called "thrombocyte."

**Prognosis.** The probable outcome or expected course of a disease. The likelihood of recovery or recurrence of disease.

**Quantitative Polymerase Chain Reaction (qPCR).** A technique to expand trace amounts of DNA so that the specific type of the DNA can be examined. This technique has become useful in detecting a very low concentration of residual blood cancer cells that cannot be seen using a microscope. A qPCR test can detect the presence of one blood cancer cell among 500,000 to 1,000,000 healthy blood cells.

**Red Blood Cell.** A type of blood cell that contains hemoglobin, which carries oxygen to the tissues of the body. Red blood cells make up about 40 to 45 percent of blood volume in healthy people. Also called "erythrocyte."

**Reduced-Intensity Stem Cell Transplantation.** A type of allogeneic transplantation. In reduced-intensity stem cell transplantation (also called "nonmyeloablative" stem cell transplantation), patients receive lower doses of chemotherapy drugs and/or radiation to prepare for the transplant. The chemotherapy and radiation do not completely kill all of the leukemia cells. Instead, the new immune cells that the patient receives in the transplant may attack the leukemia cells. This type of transplant may be safer than a regular allogeneic stem cell transplant, especially for older patients. See the free LLS publication, *Blood and Marrow Stem Cell Transplantation*.

**Refractory.** This term is used to refer to a disease that has not responded to the initial treatment. A disease that is refractory may get worse or remain stable.

**Relapse.** A return of the disease after a period of improvement.

**Remission.** When signs of a disease disappear. Remission usually follows treatment. The words “complete” and “partial” are sometimes used to further define the term “remission.” Complete remission means that all evidence of the disease is gone. Partial remission means that the disease is markedly improved by treatment, but residual evidence of the disease is present.

**Resistance to Treatment.** When cancer cells continue to grow even after administration of strong drugs and/or treatments. The cancer cells may be resistant to the drug at the beginning of treatment or may become resistant after being exposed to the drug over time.

**Response to Treatment.** An improvement related to treatment.

**Sokal Scoring System.** A scoring system used for patients with chronic myeloid leukemia that estimates their survival. Patients are designated “low-risk,” “intermediate-risk” or “high-risk” based on their spleen size, platelet count, age and the percentage of blast cells in their peripheral blood.

**Spleen.** An organ in the left upper portion of the abdomen, just under the left side of the diaphragm, that acts as a blood filter.

**Stem Cell Transplantation.** See Allogeneic Stem Cell Transplantation.

**Stem Cell.** A primitive bone marrow cell that matures into a red blood cell, a white blood cell or a platelet. Stem cells are mostly found in the bone marrow but some leave the bone marrow and circulate in the bloodstream. Stem cells can be collected, preserved and used for stem cell therapy. See Hematopoiesis.

**Translocation.** A genetic abnormality in which a piece of one chromosome breaks off and attaches to another chromosome. Sometimes genetic material is exchanged between two different chromosomes. When a translocation takes place, the gene at which the break occurs is altered. See Mutation; Philadelphia Chromosome.

**Tyrosine Kinase.** A type of enzyme that plays a key role in cell function, including cell growth and division. It is normally present in cells, and the *ABL1* gene on chromosome 9 directs its production. In CML, an alteration in the DNA results in a mutant fusion gene, *BCR-ABL1*, which produces an abnormal or mutant tyrosine kinase. This abnormal enzyme signals blood stem cells to produce too many granulocytes (white blood cells). These particular granulocytes have the *BCR-ABL1* gene and are called “leukemia cells.”

**Tyrosine Kinase Inhibitor (TKI).** A type of drug that blocks the action of enzymes called "tyrosine kinases" that are made by the *BCR-ABL1* gene so that the enzymes cannot signal the leukemia cells to grow. This specific approach to cancer therapy is referred to as "molecular-targeted therapy" because the drug is designed to block the effect of a specific protein that is the essential cause of the leukemic transformation.

**White Blood Cell.** A blood cell that is part of the body's immune system. The five types of these infection-fighting cells in the blood are neutrophils, eosinophils, basophils, monocytes and lymphocytes. White blood cells are also called "leukocytes."

# More Information

**For information about diagnosis and treatment guidelines, visit:**

European LeukemiaNet at www.leukemia-net.org. Choose leukemias in the top navigation bar and then select CML.

National Comprehensive Cancer Network at www.nccn.org/patients. Choose NCCN Guidelines for Patients on the top navigation bar.

**Information on the various risk scoring systems for CML is available on European LeukemiaNet's website at www.leukemia-net.org.**

European Treatment and Outcomes Study Score
Choose leukemias in the top navigation bar, select CML on the left navigation bar and then choose EUTOS Score on the left navigation bar.

Sokal and Hasford (also known as "Euro") Scores
Choose leukemias in the top navigation bar, select CML on the left navigation bar and then choose Euro- and Sokal-Score on the left navigation bar.

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