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Chronic Myeloid Leukemia

Revised **2020**

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

In the United States, approximately 8,450 new cases of CML are expected to be diagnosed in 2020. As of 2016, the latest year for which statistics are available, an estimated 51,342 people are either living with or in remission from CML.[1] See *Incidence, Causes and Risk Factors* on page 42.

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 select patients who meet specific criteria have the option of discontinuing treatment once their disease is in remission.

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 and treatment options for CML in clinical trials.

We are here to help.

All LLS publications mentioned in this booklet are free and can be viewed, downloaded or ordered online at www.LLS.org/booklets.

Source: *Facts 2019-2020*. The Leukemia and Lymphoma Society. April 2020.

Feedback. Visit www.LLS.org/PublicationFeedback to access the LLS Survey and give suggestions about this booklet.

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 that 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.

Leukemia is classified as either “acute” or “chronic.” These two terms describe how quickly the disease progresses without 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 43. 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 indicates whether the disease progresses quickly or slowly (acute or chronic) and also identifies the type of white blood cell that is involved (myeloid or lymphoid). The four major types of leukemia are:

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

What Is CML?

Chronic myeloid leukemia (CML) is a type of leukemia that progresses slowly 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

The World Health Organization (WHO) classifies CML as a "myeloproliferative neoplasm," a type of disease in which the bone marrow makes too many white blood cells. CML usually gets worse slowly over time, as the extra cells build up in the blood and/or bone marrow. The accumulation of white blood cells may eventually cause fatigue, bleeding and other problems. If not treated correctly, at some point, CML can turn into an acute leukemia, which is much more difficult to treat.

Visit www.LLS.org/booklets to see 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, each made up of one chromosome from each parent, for a total of 46 chromosomes. 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 in 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 make new copies of themselves to replace worn-out cells. This process is called "cell division." 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 this process. One type of error is a "translocation," which occurs when a piece of one chromosome breaks off and attaches to another chromosome. This results 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. As a result, chromosome 9 is longer than normal and chromosome 22 is shorter than normal. The abnormal chromosome 22 is known as the "Philadelphia chromosome" (because it was discovered at the Wistar Institute in Philadelphia).

Visit www.LLS.org/booklets to see the free book *Understanding Genetics.*

More than 95 percent of CML patients have the Philadelphia chromosome (see **Figure 1** on page 5). In these cases, the disease is referred to as "Ph positive (Ph+) CML" ("Ph" is the abbreviation for the Philadelphia chromosome, and the plus sign indicates the presence of the abnormal Ph chromosome.) A very small number of CML patients have the *BCR-ABL1* gene but no detectable Philadelphia (Ph) chromosome. This is called Ph-negative (Ph-) CML, in which the negative sign indicates absence of the Ph chromosome. Patients with Ph- CML have the same prognosis (likely outcome) as patients with Ph+ CML.

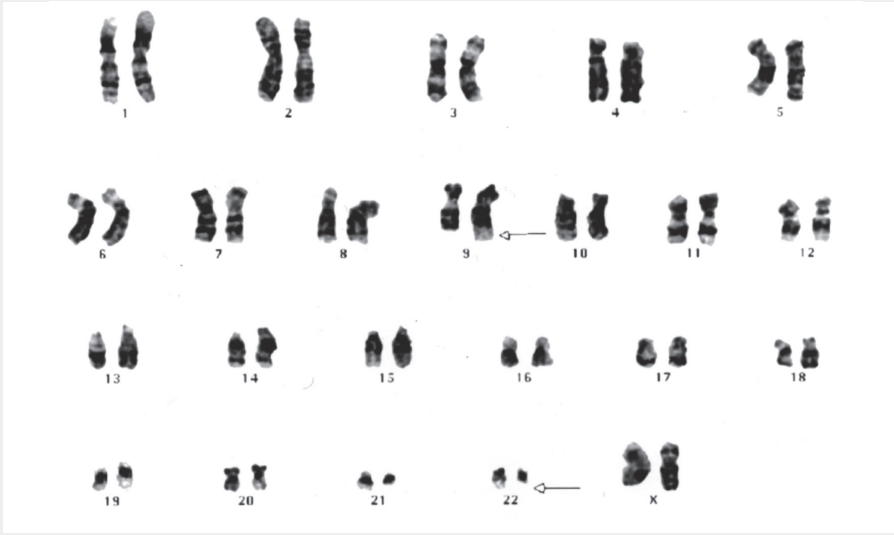
The short piece of chromosome 9 has the *ABL1* gene (named for the scientist Herbert Abelson, who discovered a similar gene in a virus that causes leukemia in mice). The break on chromosome 22 involves a gene called *BCR*, which stands for "breakpoint cluster region." Part of the *ABL1* gene moves to chromosome 22 and fuses with the first portion of the *BCR* gene. The leukemia-causing fusion gene, or "oncogene," that results from this translocation is 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 instruct 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 that signals blood stem cells to produce too many granulocytes (a type of white blood cell). These granulocytes all have the *BCR-ABL1* oncogene that causes CML and are therefore referred to as "leukemia cells" or "CML cells."

Stem cells with the *BCR-ABL1* gene (CML stem cells) divide faster than normal stem cells, leading to a constant overproduction of granulocytes. This causes high white blood cell counts and an enlarged spleen. Over time, additional mutations occur in some of the CML stem cells, which prevent them from maturing into normal white blood cells. Immature cells, called "blast cells" or "blasts," 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 of CML. See *CML Phases and Prognostic Factors* on page 9.

There is another, similar type of leukemia in which too many granulocytes are made in the bone marrow. However, the leukemia cells in patients with this disease do not have the Ph chromosome or the *BCR-ABL1* gene. These patients may be diagnosed as having "atypical CML," a disease caused by other oncogenes, and they generally have poorer responses to treatment and shorter survival times. It is very important not to confuse a diagnosis of atypical CML with other CML diagnoses, even though the leukemia cells may look quite similar when examined under the microscope.

Figure 1. Marrow Cell Chromosomes

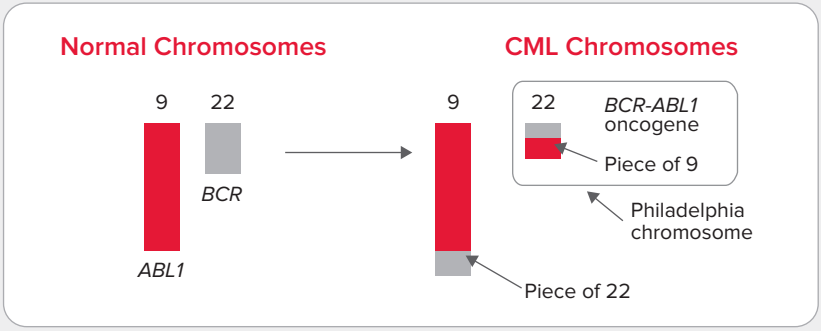


Shown here is the set of chromosomes from a marrow cell of a female patient with CML. The higher the chromosome number, the smaller the chromosome. The arrow in the fourth row indicates the shortened arm of chromosome 22 (the Ph chromosome), characteristic of the leukemic marrow cells of patients with 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

Translocation of chromosomes 9 and 22



- 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 an oncogene called *BCR-ABL1*.
- The *BCR-ABL1* oncogene 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 acute 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, some patients with CML 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 lack of red blood cells that can cause weakness, fatigue and shortness of breath. A lack of normal white blood cells can increase the risk of infection, and a lack of platelets can lead to excessive bruising or bleeding. Symptoms may also occur because CML cells accumulate 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 blood and bone marrow diseases.

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 to a very high level
- A decreased red blood cell count
- An increased or decreased platelet count, depending on the severity of the disease

Peripheral Blood Smear. In this test, blood cell samples are stained (dyed) and examined under a microscope. These samples show:

- The number, size, shape and type of blood cells
- The composition 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.

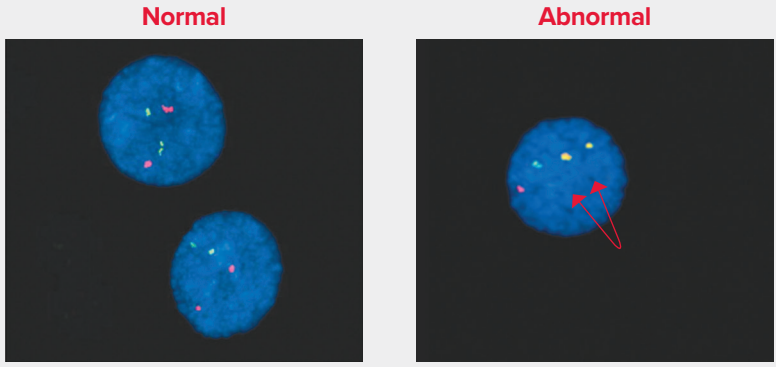
Bone Marrow Aspiration and Biopsy. These two procedures are used to obtain bone marrow cell samples, which are sent to the lab for testing to find abnormalities. They are generally done at the same time. In both cases, after medicine has been given to numb the skin and the outside of the pelvic bone, 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, a wider gauge needle removes a small sample of bone that contains marrow. Both samples are examined under a microscope. The various types of white blood cells, red blood cells and platelets are counted and examined to check their composition, and determine whether the cells look abnormal. **Visit www.LLS.org/3D to view an interactive 3D image which will help you visualize and better understand the bone marrow aspiration and biopsy procedures.**

Cytogenetic Analysis. Cytogenetics is the study of chromosomes and chromosomal abnormalities. In these tests, special stains are applied to a bone marrow sample and then the cells are examined 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, these patients almost always test positive for the *BCR-ABL1* fusion gene on chromosome 22, found with the other types of tests, such as FISH and qPCR.

Fluorescence In Situ Hybridization (FISH). This laboratory test is used to examine genes and chromosomes in cells. It is a slightly more sensitive method for detecting CML than the standard cytogenetic tests used to identify the Ph chromosome. FISH tests can identify the presence of the *BCR-ABL1* gene (see **Figure 3** on page 9).

Genes are made up of DNA segments. These tests use color probes that bind to DNA to locate the *BCR* and *ABL1* genes in chromosomes. The *BCR* and *ABL1* genes are marked with two different chemicals, each of which emits 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 pieces of chromosomes 9 and 22 that were translocated. The *BCR-ABL1* fusion gene is shown by the overlapping colors of the two probes.

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



Fluorescence in situ hybridization (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 used to detect and measure 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. It is capable of detecting 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 treatment. A qPCR test is recommended every 3 months initially. Even for patients with relatively deep disease remissions lasting at least 2 years, the test should be done every 3 to 6 months.

Visit www.LLS.org/booklets to see the free LLS booklet *Understanding Lab and Imaging Tests* and *Understanding Genetics.*

CML Phases 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 disease stage into account when determining a prognosis (likely outcome) and planning treatment. In CML, the stages are called "phases."

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, based primarily on the number of immature white blood cells (blasts) in the patient’s blood and bone marrow. Slightly different percentages of blast cells are used to differentiate each of the three phases of CML.

Chronic Phase. Most patients are diagnosed with CML while it is in the chronic phase. 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 and spleen size return to normal, and hemoglobin concentration improves.

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 often new chromosomal changes or other mutations occur, in addition to the Ph chromosome.

People with accelerated phase CML may have:

- More than 20 percent basophils (a type of white blood cell) in the bloodstream
- More than 15 percent, but less than 30 percent blasts in the blood and bone marrow
- Low platelet counts unrelated to treatment
- Increased spleen size
- Worsening anemia (caused by a low number 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, bone pain and night sweats. 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 acute myeloid leukemia.

People who have blast phase CML may have:

- Anemia
- A very high white blood cell count
- A very high or a very low platelet count
- 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
  - Night sweats
  - Bleeding
  - Infections

Prognostic Factors. There are other factors, in addition to the phase of CML, that affect treatment decisions and can be used to predict a patient's prognosis. These are called "prognostic factors."

The following prognostic factors for patients with CML at the time of diagnosis are also associated with a less favorable prognosis:

- 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
- Spleen size—Patients with an enlarged spleen
- Platelet count—Patients who have very high or very low platelet counts at diagnosis
- Blasts in the blood—Patients who have a high number of blasts in the blood
- Patients with increased numbers of basophils

Many of these factors are used in prognostic scoring systems to predict outcomes for patients with CML. There are three prognostic scoring systems used to determine the risk profile of patients with chronic phase CML at the time of diagnosis. They are the:

- Sokal scoring system: This score is based on the patient's age, spleen size, platelet count and the percentage of blast cells in the blood.
- Hasford scoring system: This score uses the same factors as the Sokal score but also includes the number of eosinophils and basophils circulating in blood.
- European Treatment and Outcome Study for CML (EUTOS) Long-Term Survival scoring system (ELTS): The ELTS score also uses the same factors as the Sokal system, but looks specifically at long-term survival in CML patients. This is important, since CML treatment is so effective that many patients are living longer and therefore die from other causes common in elderly people, such as heart disease.

See *More Information* on page 55 for links to web pages about these scoring systems.

Doctors use risk scores to help determine treatment decisions. The Sokal and Hasford scoring systems categorize CML patients into three groups: low risk, intermediate risk and high risk. Generally, patients in the low-risk category are likely to have a better response to treatment.

Treatment Options

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

Before you begin treatment, you and your doctor will discuss your treatment options. One option may be participation in a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all of your treatment options, including clinical trials, you will be taking an active role in the very important decision-making process that affects you.

Patients with CML should be treated by "hematologist-oncologists," doctors who have special training in diagnosing and treating blood cancers. 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 have achieved extremely deep disease remissions. Some of these patients have been able to discontinue treatment with careful monitoring, based on molecular testing, and their disease has remained in remission without further treatment (see *Treatment-free Remission*

on page 34). With current drug therapies, most people diagnosed with CML in the chronic phase can expect to have good quality of life for a normal life span.

CML treatment has improved dramatically since the introduction of tyrosine kinase inhibitors (TKIs). This included United States Food and Drug Administration (FDA) 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 use of TKIs has transformed CML from being a potentially fatal disease 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—in terms of dosage, form, safety, strength, route of administration, quality, performance characteristics and intended use—as a brand-name drug that is already on the market. 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 FDA employs strict standards to ensure that generic drugs are bioequivalent to brand name drugs in the United States. Generic equivalents of TKIs have been available since 2016. Talk to your doctor about which treatment option is best for you.

CML treatment can cause side effects. Most patients can manage their side effects without stopping treatment. Before you start treatment, talk with your doctor about potential side effects, other conditions that may affect your quality of life and realistic expectations about how they can be managed.

The approach for treating each patient and the choice of treatment is based on the phase of CML at diagnosis, risk scores/groups, age and the patient's other health issues. For a list of drugs used to treat CML, see **Table 1** on page 14.

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 with Ph+ CML in chronic phase 2. Patients in chronic, accelerated or blast phase with Ph+ CML, after failure of interferon-alfa therapy
Dasatinib (Sprycel®)	TKI	1. Newly diagnosed adults with Ph+ CML in chronic phase 2. Adults in chronic, accelerated or blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib 3. Pediatric patients age 1 year and older with Ph+ CML in chronic phase
Nilotinib (Tasigna®)	TKI	1. Newly diagnosed adults with Ph+ CML in chronic phase 2. Adults in chronic or accelerated phase Ph+ CML resistant to or intolerant to prior therapy that included imatinib 3. Newly diagnosed pediatric patients age 1 year and older with Ph+ CML in chronic phase 4. Pediatric patients age 1 year and older with Ph+ CML in chronic phase resistant or intolerant to prior TKI therapy
Bosutinib (Bosulif®)	TKI	1. Newly diagnosed adults with Ph+ CML in chronic phase 2. Adults in chronic, accelerated or blast phase Ph+ CML with resistance or intolerance to prior therapy
Ponatinib (Iclusig®)	TKI	1. Adults patients with chronic phase, accelerated phase, or blast phase CML for whom no other TKI is indicated 2. Adults with the T315I mutation
Omacetaxine mepesuccinate (Synribo®)	Protein synthesis inhibitor	Adults in chronic or accelerated phase CML with resistance and/or intolerance to 2 or more TKIs

The following drugs were used as initial therapy before TKIs were introduced and 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.

Lowering High White Blood Cell Counts. Some patients with CML have a very high white blood cell (WBC) count, which is discovered during diagnostic testing. An elevated WBC count can sometimes impair blood flow to the brain, lungs, eyes and other areas of the body. Even if the diagnosis of CML has not been confirmed, it can be important to lower the WBC count quickly.

- **Hydroxyurea (Hydrea®)** is sometimes given to rapidly lower a very high WBC count, until a suspected CML diagnosis can be confirmed. Hydroxyurea is taken orally as a capsule. 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 blood. It is used to lower WBC counts immediately in all patients who have a dangerously high WBC count. It is also 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. See *Fertility, Pregnancy and TKIs* on page 38.

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" or "first-line" treatment. The following four TKI drugs are approved as first-line treatment for chronic phase CML:

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

The initial treatment may not work because of drug intolerance (intolerable side effects from a particular drug), or because of drug resistance (meaning the disease does not respond to the drug). When an initial treatment does not work or stops working, a second treatment option is tried. If both the initial treatment and the subsequent (second-line) treatment fail to work, a third treatment option can be offered to the patient. In the case of resistance and/or intolerance to a second-line treatment, a TKI option for third-line 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. Some patients treated with TKIs have developed serious cardiac side effects, including heart attacks and changes in heartbeat rhythm. Some have developed narrowing of the arteries in

the extremities of the brain, which can cause a stroke. Many patients who develop these adverse effects also have other health problems and risk factors, including older age, high blood pressure, high cholesterol levels, diabetes and a history of cardiac disease, so careful monitoring is very important.

Imatinib mesylate (Gleevec®)

- In 2001, the 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 most people with chronic phase CML.
- The FDA has approved imatinib to treat:
  - Newly diagnosed adult and pediatric patients with Ph+ CML in chronic phase
  - Patients with Ph+ CML in blast crisis, accelerated phase or chronic phase after failure of interferon-alfa therapy
- Imatinib should be taken with a meal and a large glass of water.
- Grapefruit products may increase the amount of imatinib in the blood. Patients should avoid grapefruit, grapefruit juice and any supplement containing grapefruit extract while taking imatinib.
- 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 cell counts
    Having low levels of red blood cells, white blood cells and platelets can increase a patient's risk of anemia, infection and/or bleeding.
  - Edema (fluid retention that causes 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, and in others the drug stops working. These problems are known as drug "intolerance" and "resistance." Some patients can overcome imatinib resistance by increasing the dosage, while others 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 approved dasatinib to treat adults with:
  - Newly diagnosed Ph+ CML in chronic phase
  - Chronic, accelerated or blast phase Ph+ CML with either resistance or intolerance to prior therapy including imatinib
- The FDA approved dasatinib to treat pediatric patients 1 year of age and older with Ph+ CML in chronic phase.
- Dasatinib is an oral medication and is taken once daily, either in the morning or evening, with or without food. Patients taking an antacid medicine should take the antacid 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 that 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, mostly due to accumulation of fluid in the lungs (also known as a "pleural effusion")
  - Rash
  - Fever

- Serious side effects, include:
  - 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 (pleural effusion) or the heart

    Patients should call the doctor immediately if they get any of the following symptoms: swelling all over the body, weight gain, shortness of breath and cough (especially during low levels of physical activity or at rest) or chest pain when taking a deep breath.

In rare instances, dasatinib may increase the risk of developing 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. It is approved for use in:
  - Newly diagnosed adults with Ph+ CML in chronic phase
  - Adults with chronic phase and accelerated phase Ph+ CML that is resistant or intolerant to prior therapy that included imatinib
- Nilotinib is also approved for use in pediatric patients age 1 and older with:
  - Newly diagnosed Ph+ CML in chronic phase
  - Chronic phase Ph+ CML resistant or intolerant to 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 an oral medication, 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 they are taking, including over-the-counter medicines.
- Patients who take histamine type 2 receptor antagonists/blockers (called "H2 blockers") should take these medicines either 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 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 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 legs, heart or brain
  - Liver damage symptoms, including yellow skin and eyes (jaundice)
  - Inflammation of the pancreas, with symptoms including stomach pain with nausea and vomiting

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

Bosutinib (Bosulif®)

- Bosutinib is a second-generation TKI, taken orally, that was approved by the FDA in 2012 to treat CML. It is approved for use in adults with:
  - Newly-diagnosed chronic phase Ph+ CML
  - Chronic, accelerated or blast phase Ph+ CML with resistance or intolerance to prior therapy.
- Side effects include:
  - Stomach pain, diarrhea, nausea and/or vomiting
  - Fluid retention
  - Rash
  - Fatigue
- Serious side effects include:
  - Low blood cell counts

    Low levels of red blood cells, white blood cells and platelets that 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. It is approved for use in:
  - 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 (The T315I mutation is a genetic change in *BCR-ABL1* that makes it resistant to imatinib, nilotinib, dasatinib and bosutinib.)

    Ponatinib is not indicated and is not recommended for first-line treatment of patients with newly diagnosed, chronic phase CML.
- Ponatinib is an oral medication that 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:
  - Rash
  - Stomach-area (abdominal) pain
  - Fatigue
  - Headache
  - Dry skin
  - Fever
  - Constipation
  - High blood pressure (hypertension)
- Serious side effects and/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; headaches; severe stomach pain; dizziness; decreased vision and/or loss of vision; 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 (hypertension)
  - 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 blurred vision and/or blindness
  - 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 medications, antacids and the herbal supplement St. John's Wort can make some TKIs less effective. Some products, including certain antibiotics, antifungal medications and grapefruit products, may increase the amount of TKIs in the blood to high, unsafe levels.

In addition, 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 a TKI. It is also important to ask the doctor about any foods that should be avoided.

TKI Resistance. "Drug resistance" is the term used when a disease has not responded to treatment. Drug resistance in CML occurs when leukemia cells do not respond to a drug that is being used to treat 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. Sometimes, resistance to a TKI can be stopped by increasing the dosage 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 *BCR-ABL1 Kinase Domain Mutation Analysis* on page 32). This information can help a doctor decide which drug to prescribe.

TKI Adherence. It is important for patients to take their TKIs exactly 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

TKIs can control CML in most patients. Patients should never skip doses to try to reduce the side effects of the medication. Instead, they 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 exactly as prescribed to achieve the best response. Not adhering to the medication regimen is a primary reason for poor 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. If you can't afford your medication and are not taking the prescribed amount, talk to your healthcare team. **Visit www.LLS.org/finances for more information.**

Chemotherapy. The use of chemotherapy is limited in CML treatment. Generally, it is only used in patients with blast phase CML in order to return the disease to the chronic phase. In addition, very high-dose chemotherapy is used as preparation for an allogeneic stem cell transplant in CML patients who receive this treatment.

Omacetaxine mepesuccinate (Synribo®), a protein synthesis inhibitor, is a treatment option for adult patients with chronic or accelerated phase CML with resistance and/or intolerance to 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 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 made naturally 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 the 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 TKIs are more effective and have fewer side effects. Interferon may be an option for patients who cannot tolerate the side effects of TKI therapy, or patients who are pregnant.

Interferons 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 interferon treatment.

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

Allogeneic Stem Cell Transplantation. For certain patients with CML, allogeneic stem cell transplantation (the infusion of donor stem cells into a patient) is their best treatment option. 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 of transplants using stem cells from matched sibling donors are very similar to those of transplants that use stem 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 stem cell transplantation has been proven to be curative for some CML patients, treatment with TKIs may control the disease for very long periods and preserve quality of life without the serious side effects of transplantation.

Doctors 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, phase of CML, history of poor response to other treatments and the availability of a well-matched donor. Stem cell 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 post-transplant survival 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 see the free LLS booklet *Blood and Marrow Stem Cell Transplantation* for more information about all types of stem cell transplants.

Treating CML by Phase

Each phase of CML requires a different treatment approach.

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

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

When choosing a first-line TKI, doctors may consider factors such as a patient's pre-existing health conditions, age and risk score/group, as well as the dosing schedule and drug cost. After treatment starts, doctors will monitor patients to evaluate treatment response. Patients who are responding well will stay on their 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 should be done to check for mutations of the *BCR-ABL1* gene (see *BCR-ABL1 Kinase Domain Mutation Analysis* on page 32). 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, and sometimes **ponatinib (Iclusig®)**
- Trying other therapies (such as **omacetaxine mepesuccinate (Synribo®)**, 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 treatment goal for accelerated phase CML is the same as it is for the chronic phase: 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. Patients with accelerated phase CML should be treated at a specialized center, with doctors who have expertise in treating CML.

In the accelerated phase of CML, the leukemia cells often acquire new genetic mutations that may make treatments less effective. Patients should undergo

BCR-ABL1 gene mutation analysis before starting treatment, to determine which treatment option is best for them (see *BCR-ABL1 Kinase Domain Mutation Analysis* on page 32).

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, the best treatment option is to begin TKI therapy. The drugs approved for TKI therapy include:

- Imatinib
- Dasatinib
- Nilotinib
- Bosutinib

If 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:

- Ponatinib (Iclusig®) for the treatment of adult patients with chronic phase, accelerated phase, or blast phase CML for whom no other TKI therapy is indicated.
- Omacetaxine mepesuccinate (Synribo®) (only an option for patients who have experienced resistance or intolerance to two or more TKIs)
- An allogeneic stem cell transplant
- 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 39.

Treatment for Blast Phase CML. The leukemia cells in patients with blast phase CML have become very abnormal. Blast phase CML is similar to an acute leukemia, with higher blood cell counts and more severe symptoms. Patients with blast phase CML should be treated at a specialized center, with doctors who have expertise in treating CML.

The following 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, called "flow cytometry," is important because the type of blast cells is a factor in treatment decisions.
- The second test, a *BCR-ABL1* kinase domain mutation analysis, checks for mutations in the part of the *BCR-ABL1* gene that is targeted by TKIs (see

BCR-ABL1 Kinase Domain Mutation Analysis on page 32). Different mutations can make the BCR-ABL1 protein either more or less resistant to certain TKIs (such as ponatinib, which can be prescribed for patients with the T315I mutation).

One option for patients with blast phase CML is to receive treatment in a clinical trial. 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 39.

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 or ponatinib are preferred treatments for blast phase CML. Patients who respond to these drugs should consider undergoing allogeneic stem cell transplantation, which offers the best chance of a long-term remission. 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 in a disease 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 31 describes the different types of treatment responses for CML. There are three types of response: hematologic, cytogenetic and molecular.

Hematologic Response. This response is classified 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 (as well as the different types of white blood cells) and platelets in the blood.

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

Cytogenetic Response. This response is identified based on a measurement of the number of cells (percentage) in the bone marrow that contain the Ph chromosome (Ph+ cells). Either cytogenetic analysis or a FISH test is used to measure the number of these cells. Cytogenetic analysis of bone marrow cells (bone marrow cytogenetics) is done at 3-month intervals to check the patient's response to treatment, if a reliable qPCR test is not available (see *Quantitative Polymerase Chain Reaction* on page 9).

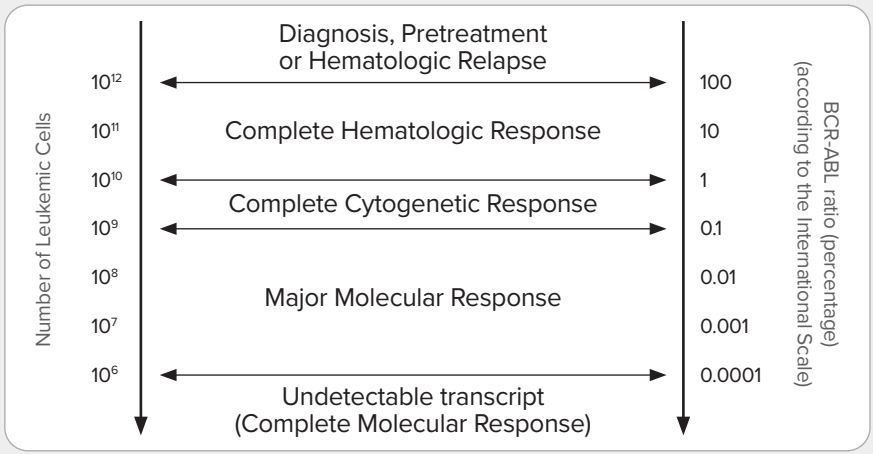
- Minor cytogenetic response—The Ph chromosome is found in more than 35 percent of cells in the bone marrow.
- Major cytogenetic response (MCyR)—There are 35 percent or fewer cells with the Ph chromosome. This term is sometimes used to describe either a complete or partial cytogenetic response.
- Partial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

Molecular Response. A molecular response is a decrease in the number of cells with the *BCR-ABL1* gene. A qPCR test is used to measure the number of cells in the blood that contain the *BCR-ABL1* gene and is explained as a percentage. A patient's initial molecular response to treatment is significant in predicting outcome and in determining further treatment options. Molecular response is the most sensitive method of monitoring *BCR-ABL1* levels in the blood.

- Early molecular response (EMR)—The *BCR-ABL1* level is 10 percent or less at 3 and 6 months after the start of treatment. This means that the leukemia cells have been reduced by 90 percent or more.
- Major molecular response (MMR)—The *BCR-ABL1* level has decreased to 0.1 percent. This means that the leukemia cells have been reduced by 99.9 percent or more.
- Deep molecular response (DMR)—The *BCR-ABL1* level has decreased to 0.01 percent or less.
- Undetectable/Complete Molecular Response (CMR)—The *BCR-ABL1* level can't be detected.

The International Scale (IS). This is a standardized scale for measuring qPCR test results. The qPCR test reflects the number of cells that have the *BCR-ABL1* gene. It is used to determine how well treatment is working. The International Scale (IS) defines the standard baseline as *BCR-ABL1* 100 percent. (This baseline was developed from the IRIS clinical trial, by testing a large number of patients' pretreatment samples and normalizing the average patient results to create this baseline.) The term "baseline" refers to the start of treatment. The International Scale baseline is standardized and is used for all CML patients. See **Figure 4** on page 29.

Figure 4. Treatment Response International Scale



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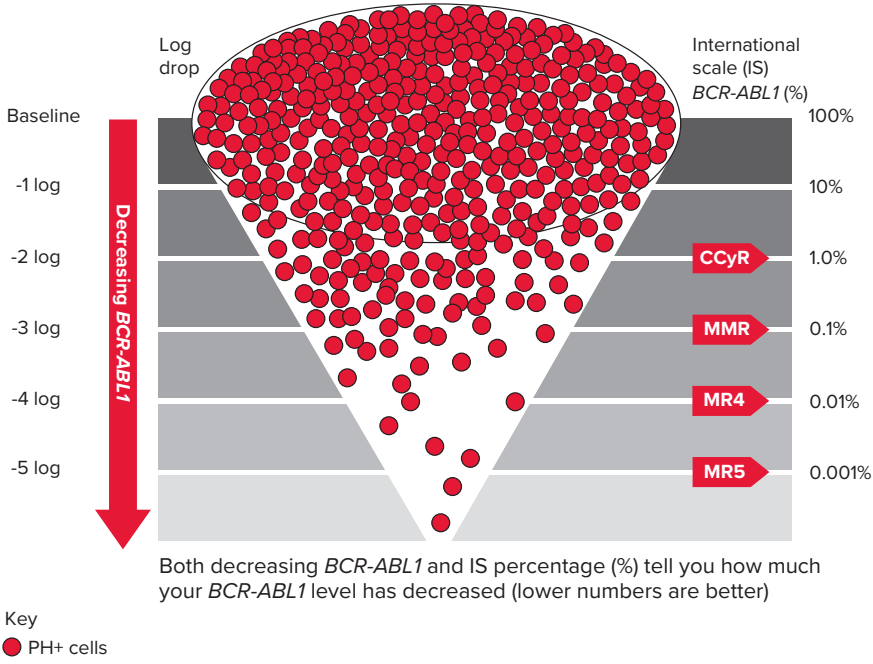
Log Reduction. A log reduction indicates the *BCR-ABL1* level has decreased by a certain amount from the standard baseline. For example, a 1-log reduction indicates the BCR-ABL1 level has decreased by 90 percent, a 2-log reduction by 99 percent, and so forth as described on page 29 and **Figure 5** on page 30.

- 1-log reduction means that the *BCR-ABL1* level has 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 reduction is equivalent to an early molecular response when achieved within 3 to 6 months of starting treatment.
- 2-log reduction means that the *BCR-ABL1* level has 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.
- 3-log reduction means that the *BCR-ABL1* level has 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. It is also known as a "major molecular response (MMR)."
- 4-log reduction means that 0.01% of cells (1 out of every 10,000 cells) have the *BCR-ABL1* gene.
- 4.5-log reduction is referred to as a "complete molecular response (CMR)" or a "deep molecular response (DMR)." 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 TKI therapy, under careful medical supervision. See *Treatment-Free Remission* on page 34.

- 5-log reduction means that 0.001% of cells (1 out of every 100,000) have the *BCR-ABL1* gene. By reaching a 5-log reduction, patients have achieved "undetectable *BCR-ABL1*."

Figure 5. Treatment Response by Log Reduction



Key. CCyR, complete cytogenic response; IS, International Scale; log, logarithm; MMR, major molecular response; MR4, molecular response 4; MR5, molecular response 5; PH+, Philadelphia [chromosome] positive.

Unfortunately, qPCR tests cannot be completely standardized from laboratory to laboratory. Different laboratories may establish their own standardized baseline values. So, slightly different results may be obtained at different labs based on the same patient sample. 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.

It is recommended that patients get a qPCR test done every 3 months initially. After 2 years of achieving and maintaining a *BCR-ABL1* level of 0.1 percent or less, the test should be done every 3 to 6 months.

Table 2. Chronic Myeloid Leukemia Treatment Responses

Type of Response		Features	Test Used to Measure Response
Hematologic	Complete hematologic response (CHR)	• Blood cell counts completely return to normal • No blasts in the peripheral blood • 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	Early molecular response (EMR)	*BCR-ABL1* level has been reduced by 90 percent or more	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%	
	Deep molecular response (DMR)	At least a 4-log reduction, 4.5-log reduction or 5-log reduction	
	Undetectable/ Complete Molecular Response (CMR)	No *BCR-ABL1* gene detected	

A 3-log reduction is a 1/1,000 or 1,000-fold reduction of the level of cells with the *BCR-ABL1* gene. See *Log Reduction* on page 28.

Treatment responses for CML. Source: NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia, version 3.2020

BCR-ABL1 Kinase Domain Mutation Analysis

In CML, mutations in the *BCR-ABL1* gene 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. 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. This test should be performed if there is:

- An inadequate response to the initial TKI therapy
- A failure to meet a treatment milestone
- A loss of hematologic, cytogenetic or major molecular response, or a 1-log increase in the *BCR-ABL1* level, 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

For people with CML that stops responding to a TKI, or who do not achieve the expected response within a given period of time (see **Table 3** on page 33), the most common options are switching to another approved TKI or participating in a clinical trial. Every patient with CML responds differently to TKI therapy. These general guidelines for TKI therapy in CML patients are available online from the National Comprehensive Cancer Network (NCCN) and the European Leukemia Net (ELN). See *More Information* on page 55 for links to these and other resources.

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

Adapted from NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia; version 3.2020.
Abbreviations: MCyR, major cytogenetic response; CCyR; complete cytogenetic 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.

Treatment-Free Remission

Because of advances in the understanding of CML and the highly successful results of TKI therapy, treatment-free remission (TFR) is now an emerging treatment goal for CML patients. 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 [CMR]") and does not need to restart treatment. Many patients with CML achieve a stable, deep response to treatment with TKIs.

The feasibility and safety of discontinuing TKI therapy has been evaluated in several studies. Patients with CML in chronic phase who achieve and maintain a stable, deep molecular response (DMR) are considered good candidates for TKI therapy discontinuation, under careful medical supervision.

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

- Adult patients with newly diagnosed CML in chronic phase who were treated with **nilotinib (Tasigna®)** for at least 3 years and who have maintained molecular response 4.0 (MR4.0) 1 year prior to discontinuation of therapy
- Adult patients with CML in chronic phase who are resistant or intolerant to **imatinib (Gleevec®)** and who achieved a MR4.5 on nilotinib and who received nilotinib for at least 3 years and have achieved MR4.5 for at least 1 year

Table 4 and **Table 5**, on page 35, lists the main clinical criteria for patients who want to attempt to discontinue TKI therapy and achieve treatment-free remission.

Table 4. Clinical Criteria for TKI Discontinuation in a Newly Diagnosed Ph+ CML Chronic Phase Patient

Parameter	Criteria
Age	18 years and older
CML phase	Chronic phase only
BCR-ABL1 transcripts	e13a2/b2a2 or e14a2/b3a2
TKI treatment duration (nilotinib)	At least 3 years
Molecular response	Maintained MR4.0 for one year prior to discontinuation
DMR duration	Achieved in last test prior to discontinuation
Prior treatment history	No history of accelerated or blast crisis; no history of prior attempts of treatment-free remission discontinuation that resulted in relapse.

This table shows the clinical criteria for TKI therapy discontinuation in patients with newly diagnosed Ph+ CML-CP. Adapted from Tasigna Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/tasigna.pdf
Abbreviations: CML-CP, chronic myeloid leukemia-chronic phase; DMR, deep molecular response; MR4.0, molecular response of 4.0-log reduction on the International Scale, indicating complete molecular response; Ph+, Philadelphia [chromosome] positive; TKI, tyrosine kinase inhibitor.

Table 5. Clinical Criteria for TKI Discontinuation in a Ph+ CML Patient Who is Resistant or Intolerant to Treatment with Imatinib

Parameter	Criteria
Age	18 years and older
CML phase	Chronic phase only
BCR-ABL1 transcripts	e13a2/b2a2 or e14a2/b3a2
TKI treatment duration (nilotinib)	Minimum of 3 years and treated with imatinib only prior to treatment with nilotinib
Molecular response	MR4.5
DMR duration	Sustained MR4.5 for a minimum of one year immediately prior to discontinuation of therapy
Prior treatment history	No history of accelerated or blast crisis; no history of prior attempts of treatment-free remission discontinuation that resulted in relapse

This table shows the clinical criteria for TKI therapy discontinuation in patients with Ph+ CML-CP that are resistant or intolerant to treatment with imatinib who have achieved a sustained molecular response (MR4.5) on Tasigna. Adapted from Tasigna Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/tasigna.pdf
Abbreviations: CML-CP, chronic myeloid leukemia-chronic phase; DMR, deep molecular response; MR4.5, molecular response of 4.5-log reduction on the International Scale, indicating complete molecular response; Ph+, Philadelphia [chromosome] positive; TKI, tyrosine kinase inhibitor.

CML patients have many reasons to attempt treatment-free remission. Motivations may include convenience, reducing medical expenses 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 is 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 booklet *Treatment-Free Remission for Chronic Myeloid Leukemia Patients*.

Children and Young Adults

Most cases of CML occur in adults. From 2012 to 2016, approximately 2 percent of all cases of CML occurred in children, adolescents and young adults less 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 Ph+ CML in chronic phase
  - Ph+ CML in chronic phase resistant or intolerant to prior TKI therapy

Children with CML may receive TKI therapy for a much longer time than adults, so during periods of active growth, follow-up care is very important. In addition to evaluating treatment response, doctors should also monitor the following concerns 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 exactly 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 poor response and treatment failure.

Taking into account the potential concerns of lifelong TKI treatment, researchers are studying TKI discontinuation in pediatric and young adult CML patients 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 *Treatment-Free Remission* on page 34). 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 used only in cases of relapse or accelerated/blast phase CML. Due to the small number of pediatric patients, there have been no randomized, controlled trials comparing stem cell transplantation with imatinib use in children. Because of this, decisions about treatment approaches in children with CML must be individualized. The complications of stem cell transplantation must be weighed against the complications associated with lifelong TKI use.

A clinical trial may be the best treatment option. 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 see the free LLS booklets *Choosing a Blood Cancer Specialist or Treatment Center* Facts. Visit www.LLS.org/FamilyWorkbook for additional information about coping with a blood cancer. Visit www.LLS.org/CTSC to learn more about clinical trials and to contact a Clinical Trial Nurse Navigator.

Fertility, Pregnancy and TKIs

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

Growing numbers of CML patients of childbearing age are living in stable remissions and are considering having children while being treated for CML. There is no risk that parents will pass the Ph chromosome onto their children.

Generally, there are no concerns for men on TKIs associated with having children. Sperm counts tend to improve 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. Therefore, women of childbearing age must use effective contraception while on TKI therapy.

If a woman is considering pregnancy during TKI therapy, early consultation with her hematologist-oncologist, as well as a high-risk obstetrician, is mandatory. They need 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 suspend TKI therapy prior to conception and during the pregnancy, then resume it immediately after the birth of her child and refrain from breastfeeding. The patient should be closely monitored with qPCR tests for signs of disease progression during pregnancy. 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, no data suggest that either imatinib or any other TKI drug can be taken safely during pregnancy. Current recommendations include counseling so that the potential parents understand the:

- Risk of relapse in women who discontinue TKI 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, stable response to treatment. Female patients who are interested in having children should discuss all their options with their treatment team, including the possibility of TKI discontinuation to try for treatment-free remission. See *Treatment-Free Remission* on page 34.

Research and Clinical Trials

Every new drug or treatment regimen goes through a series of studies called "clinical trials" before it becomes part of the standard treatment for a disease. 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 available through 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 US Food and Drug Administration (FDA).

There are clinical trials for patients who have not yet received an initial treatment, patients who have already received treatments 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 given in combination with 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. The following drug therapies and combinations are being evaluated for use in CML treatment:

- **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.
- **Ruxolitinib (Jakafi®)** is a pan-Janus kinase inhibitor. It is already approved to treat patients who have been diagnosed with myelofibrosis or polycythemia vera.
- **Ipilimumab (Yervoy®)** is a monoclonal antibody and also an immune checkpoint inhibitor that is currently being evaluated.
- **A tyrosine kinase inhibitor in combination with interferon alpha.** Several studies have shown improved molecular response rates in CML patients using this combination.

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), continues to be evaluated in several long-term studies. (TKI discontinuation can also occur outside of a clinical trial, under certain circumstances.) See *Treatment-Free Remission* on page 34.

Reduced-intensity Conditioning Allogeneic Stem Cell Transplantation. This modified form of allogeneic transplantation (also known as 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 therapy in preparation for the transplant, compared to the doses given to patients receiving a traditional allogeneic stem cell transplant. The theory being tested with a

reduced-intensity transplant is that: 1) by undergoing less toxic procedures prior to the transplant, the body is better able to withstand the transplant; and 2) full donor engraftment and the desired graft-versus-leukemia effect would still occur. Ongoing clinical trials are evaluating the use of this type of stem cell 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

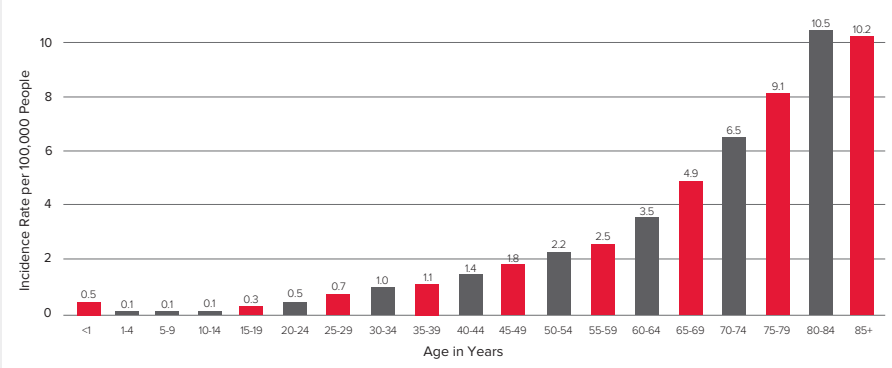
CML follow-up care varies from patient to patient. However, all CML patients:

- Will need to see their doctor on a regular basis. The doctor will evaluate their health, check blood cell counts and their molecular response 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. Patients with CML can receive the shingles vaccine **Shingrix**®, because it is an inactivated rather than a live form of the vaccine. Your doctor can give you more information.
- Always need to keep good records and treatment notes, including:
  - 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 2012-2016 the incidence of CML in the United States was 1.9 per 100,000 men and women (see **Figure 6** below). This disease 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 over the age of 80. The median age at diagnosis is 65 years. A small number of children develop CML (see *Children and Young Adults* on page 36).

Figure 6. Age-Specific Incidence Rates for Chronic Myeloid Leukemia (CML), 2012-2016



The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of CML per 100,000 people, by age-group.
Source: *SEER (Surveillance, Epidemiology, and End Results) Cancer Statistics Review, 1975-2016.* National Cancer Institute; 2019.

Causes. CML is not passed from parent to child, so no one is born with CML. Rather, it occurs when there is an injury (mutation) to the DNA of a single bone marrow cell. The mutated cell, referred to as a "leukemia" or "CML" 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 people often have no 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 generally been associated with an increased risk of CML. CML has been reported in individuals undergoing excessive diagnostic X-rays or computed tomography (CT) scans so every X-ray or CT scan needs to be well justified to minimize the risk of CML and other types of leukemia.

Normal Blood and Bone Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients throughout the body. It also carries away waste products. Blood is composed of plasma and cells.

Plasma. Plasma is largely made up of water, in which many chemicals are dissolved. These chemicals each have a special role. They include:

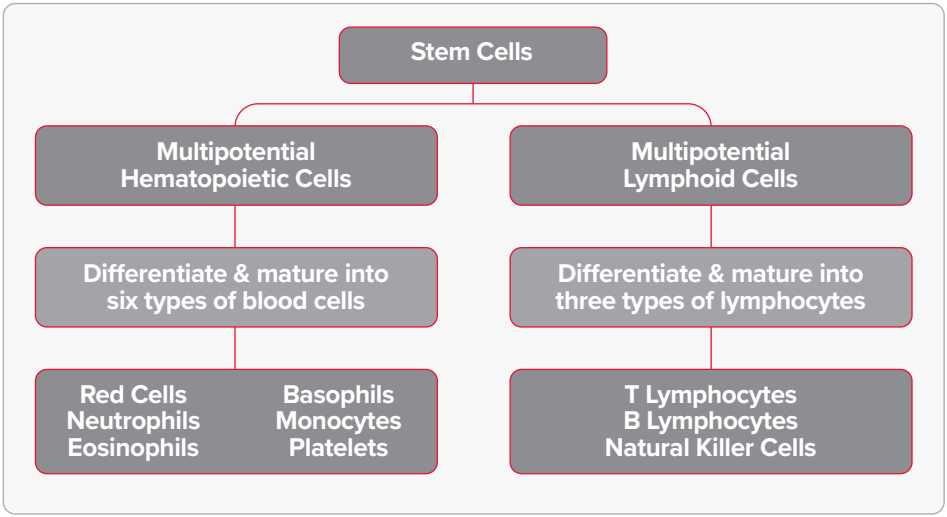
- Proteins
  - Albumin, the most common blood protein
  - Blood-clotting proteins (coagulation factors) made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
  - Immunoglobulins, proteins that help the body fight infection
- Hormones, such as thyroid hormone and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B_{12}
- Electrolytes, such as calcium, potassium and sodium

Blood cells. Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called "hematopoiesis." The blood cells are suspended in the plasma. See **Figure 7** on page 45.

Once the stem cell is created, it will develop into one of the three types of blood cells:

1. Red blood cells (the cells that carry oxygen)
    - These make up a little less than half of the body's total blood volume.
    - They are filled with hemoglobin, the protein that picks up oxygen from the lungs and takes it around the body. It binds with carbon dioxide (CO_2) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO_2 is removed from the lungs.
2. Platelets (cells that help blood to clot)
    - These are small cells (one-tenth the size of red blood cells).
    - They help stop bleeding from an injury or cut.
    - They stick to the torn surface of the vessel, clump together and plug up the bleeding site. They form a clot with the help of proteins, such as fibrin, and electrolytes, such as calcium.
3. White blood cells (WBCs). These are the cells that fight infections. They include:
    - Neutrophils and monocytes. These cells, called "phagocytes," ingest and destroy bacteria and fungi. Unlike red blood cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
    - Eosinophils and basophils. These WBCs respond to allergens or parasites.
    - Lymphocytes. These WBCs, found mostly in the lymph nodes, spleen and lymphatic channels, are a key part of the immune system. Some enter the bloodstream. There are three major types of lymphocytes:
        - T lymphocytes (T cells)
        - B lymphocytes (B cells)
        - Natural killer cells (NK cells)

Figure 7. Blood Cell & Lymphocyte Development



Stem cells develop into blood cells (hematopoiesis) and lymphocytic cells.

Bone Marrow. In healthy people, stem cells in the bone marrow produce new blood cells continuously. When blood cells are fully developed, they enter the bloodstream as it passes through the marrow and then circulates throughout the body.

In babies, 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 blood-forming marrow. In adults, marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull.

Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be used for transplants. Some stem cells enter the bloodstream and circulate. Doctors know how to stimulate the growth of these cells in the marrow and make them migrate into the bloodstream. Then a special technique called "apheresis" is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

Resources and Information

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

For Help and Information

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

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

Clinical Trial 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 a clinical trial according to their needs 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 be either 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 with 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 eligible patients. Please call or visit our website for more information.

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

Free Mobile Apps

- LLS Coloring For Kids™ – Allows children to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit www.LLS.org/ColoringApp to download for free.
- LLS Health Manager™ – Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit www.LLS.org/HealthManager to download for free.

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

Continuing Education. LLS offers free continuing education programs for healthcare professionals. Please visit www.LLS.org/ProfessionalEd for more information.

Community Resources and Networking

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

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

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), local support groups and other great resources. For more information about these programs or to contact the nearest chapter, please call or visit our website.

- 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) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve

access to quality medical care. Please call or visit our website for more information.

- 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 translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information, please call the VA or visit the web page.

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

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

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

For more information, please call the WTC Health Program or visit their web page.

- Call: (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) or visit their website.

- Call: (866) 615-6464
- Visit: www.nimh.nih.gov and enter “depression” in the search box

Health Terms

ABL1. One of the genes involved in the translocation (a type of mutation) that produces the *BCR-ABL1* "fusion gene," in which it breaks off from chromosome 9 and reattaches to chromosome 22. 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 a similar gene while studying cancer-causing viruses in mice.

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

Anemia. A 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.

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" (oncogene) that causes CML. See Tyrosine Kinase.

Blast Cell. An immature (undeveloped) blood cell.

Bone Marrow. The spongy tissue in the hollow, central cavity of bones where blood cell formation occurs. 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 the bloodstream carries them throughout the body.

Bone Marrow Aspiration. A procedure done to collect a liquid sample of bone marrow cells, which is used for testing to detect cell abnormalities. The bone marrow sample is usually taken from the patient's hip bone using a special needle. It is normally done at the same time as a bone marrow biopsy.

Bone Marrow Biopsy. A procedure done to collect a solid sample of bone containing bone marrow cells, which is used for testing to detect cell abnormalities. After medication is given to numb the skin and outer bone, a special, hollow needle is used to remove the sample, 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 at the same time.

Chemotherapy. Treatment with chemical agents (medication) 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 contain genes arranged in a linear order. Human cells have 23 pairs of chromosomes.

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 doctors diagnose specific types of blood cancer, 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 in which stem cells develop into mature cells with specific functions. Stem cells mature into red blood cells, platelets or white blood cells. See Hematopoiesis.

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.

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

Graft-Versus-Leukemia Effect. Occurs when transplanted blood stem cells (the graft) perceive the leukemia cells in the patient's body as foreign and attack the cancer cells, as they are intended to do. Also called the "graft-versus-tumor effect."

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 prognostic scoring system that estimates survival of patients with chronic phase CML. The system categorizes patients into three groups: low risk, intermediate risk or high risk. Hasford scores are calculated based on the following factors for each patient at diagnosis:

- Spleen size
- Platelet count
- Age
- Percentage of blast cells circulating in the peripheral blood
- Number of eosinophils and basophils circulating in the peripheral blood

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, lymph and other tissue samples under a microscope.

Hematopoiesis. The formation and development of blood cells in the bone marrow. For more information on the blood cell development process, see *Normal Blood and Bone Marrow* on page 43.

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

Lymph Node. A bean-shaped structure that is part of the body's immune system. There are hundreds of lymph nodes located throughout the body. They 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:

- 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. A type of white blood cell that surrounds and kills microorganisms, removes dead cells and stimulates the action of other immune system cells. Also referred to as a "scavenger cell." See Monocyte.

Minimal Residual Disease or Measurable 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 forms 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 (deoxyribonucleic acid) 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.

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

Oncogene. A changed (mutated) gene that contributes to the development of cancer. Several subtypes of acute myeloid leukemia, acute lymphoblastic leukemia and lymphoma, and 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 Care. 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 diseases by examining body tissues 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 travel to the site of the infection through the bloodstream and enter the infected tissue. Chemotherapy and radiation therapy can cause a decrease in the number 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. As a result, chromosome 22 is shorter than normal. The exchange of DNA (deoxyribonucleic acid) between chromosomes 9 and 22 results in the creation of a cancer-causing gene (oncogene) called "*BCR-ABL1*" on chromosome 22.

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

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

Quantitative Polymerase Chain Reaction (qPCR). A technique used to expand trace amounts of DNA (deoxyribonucleic acid), 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 with 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 an "erythrocyte."

Reduced-Intensity Conditioning Allogeneic Stem Cell Transplantation. In this type of stem cell transplant, patients receive lower doses of chemotherapy drugs and/or radiation ("conditioning" treatment) to prepare for the transplant. The chemotherapy and radiation do not kill all of the leukemia cells. Instead, the new immune cells generated in the patient as a result of 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. Also called "nonmyeloablative stem cell transplantation." See the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

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

Relapse. When a disease returns after a period of improvement.

Remission. When signs of a disease disappear, usually following treatment. The remission is sometimes further defined as complete or partial. “Complete remission” means that all evidence of the disease is gone. “Partial remission” means that the disease is markedly improved by treatment, but evidence of the disease is still present in the body.

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 in a disease related to treatment.

Sokal Scoring System. A prognostic scoring system used to estimate the survival of patients with chronic phase CML. Patients are categorized into risk groups (low risk, intermediate risk and high risk) based on their spleen size, platelet count, age and the percentage of blast cells in their 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. An undifferentiated 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 (for example, a stem cell transplant). See Differentiation; 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 (Ph Chromosome).

Tyrosine Kinase. A type of enzyme that plays a key role in cell functions, including cell growth and division. It is normally present in cells, and certain genes (such as the *ABL1* gene on chromosome 9) direct its production. In CML, an alteration in the DNA (deoxyribonucleic acid) results in the mutant fusion gene (an oncogene) called “*BCR-ABL1*,” which produces an abnormal tyrosine kinase. This abnormal enzyme signals blood stem cells to produce too many granulocytes (white blood cells). The resulting granulocytes all have the *BCR-ABL1* oncogene and are called “leukemia cells.”

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

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

More Information

For information about diagnosis and treatment guidelines for CML, visit:

European LeukemiaNet (ELN) 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 Long-Term Survival (ELTS) Score
Choose leukemias in the top navigation bar, select CML on the left navigation bar and then choose ELTS Score on the left navigation bar.

Hasford (also known as "Euro") and Sokal 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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