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Chronic Myeloid Leukemia

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Publication Update
Chronic Myeloid Leukemia

The Leukemia & Lymphoma Society wants you to have the most up-to-date information about blood cancer treatment. See below for important new information that was not available at the time this publication was printed.

- In December 2017, the Food and Drug Administration (FDA) approved bosutinib (Bosulif®) for the treatment of adult patients with newly-diagnosed chronic phase Ph+ chronic myeloid leukemia (CML). This indication is approved under accelerated approval based on molecular and cytogenetic response rates. Continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term follow up trial.

  It is also approved for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy.

- In November 2017, the Food and Drug Administration (FDA) approved dasatinib (Sprycel®) for the treatment of pediatric patients with Ph+ CML in chronic phase.

For more information, contact an Information Specialist at (800) 955-4572 or infocenter@lls.org.

A Message from Louis J. DeGennaro, PhD

President and CEO of The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society (LLS) is the world's largest voluntary health organization dedicated to finding cures for blood cancer patients. Our research grants have funded many of today's most promising advances; we are the leading source of free blood cancer information, education and support; and we advocate for blood cancer patients and their families, helping to ensure they have access to quality, affordable and coordinated care.

Since 1954, we have been a driving force behind nearly every treatment breakthrough for blood cancer patients. We have invested more than $1 billion in research to advance therapies and save lives. Thanks to research and access to better treatments, survival rates for many blood cancer patients have doubled, tripled and even quadrupled.

Yet we are far from done.

Until there is a cure for cancer, we will continue to work hard—to fund new research, to create new patient programs and services, and to share information and resources about blood cancer.

This booklet has information that can help you understand chronic myeloid leukemia (CML), prepare your questions, find answers and resources, and communicate better with members of your healthcare team.

Our vision is that, one day, all people with CML will either be cured or will be able to manage their disease so that they can experience a great quality of life. Today, we hope our expertise, knowledge and resources will make a difference in your journey.

Louis J. DeGennaro, PhD
President and Chief Executive Officer
The Leukemia & Lymphoma Society

Inside This Booklet

Acknowledgement

The Leukemia & Lymphoma Society gratefully acknowledges for his critical review and important contributions to the material presented in this booklet,

Jerald P. Radich, MD
Clinical Research Division
Fred Hutchinson Cancer Research Center
Seattle, WA

Introduction

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

The National Cancer Institute estimates 44,386 people[1] in the United States are living with CML, with another 8,950[2] new cases expected in 2017. Some articles estimate that closer to 80,000 to 100,000 people in 2015 were living with CML.[3]

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 are living longer with CML and experiencing fewer treatment side effects.

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 often hard-to-understand terms, provides information about normal blood and bone marrow, explains tests and treatments you may encounter and lists new research options and clinical trials.

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

We are here to help.

1. Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.
2. *Cancer Facts & Figures, 2016*. American Cancer Society; 2016.
3. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2016 update on diagnosis, therapy, and monitoring. *American Journal of Hematology*. 2016;91(2):252-265.

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 that can be helpful to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team members' knowledge and skills.

For Help and Information

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

- Call: (800) 955-4572 (Monday through Friday, from 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/informationspecialists
- Visit: www.LLS.org/informationspecialists.

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

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

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

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

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

Continuing Education. LLS offers free continuing education programs for health care professionals. For more information, please visit www.LLS.org/professionalEd.

Community Resources and Networking

LLS Community. The one-stop virtual shop for chatting with other patients and staying up-to-date on the latest diagnosis and treatment news. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. To join, visit www.LLS.org/community.

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

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

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

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

Clinical Trials (Research Studies). New treatments for patients are underway. Patients can learn about clinical trials and how to access them. For more information, please call (800) 955-4572 to speak with an LLS Information Specialist who can help conduct clinical-trial searches. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

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

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

Additional Help for Specific Populations

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

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

Children. CML occurs in a small number of children. Families face new and unfamiliar treatments and care protocols. The child, parents and siblings may all need support. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/booklets to reach *Coping with Childhood Leukemia and Lymphoma*.
- Call: (800) 955-4572 to ask about *The Trish Greene Back to School Program for Children with Cancer.*

Information for Veterans. Veterans with CML 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: (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/agentorange.

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

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

For more information, please

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

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

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

Feedback. To give suggestions about this booklet, visit www.LLS.org/publicationfeedback.

Leukemia

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

- Acute myeloid leukemia
- Chronic myeloid leukemia
- Acute lymphoblastic leukemia
- Chronic lymphocytic leukemia.

Leukemia is described as either "acute" or "chronic." These classifications are determined by how quickly the disease progresses. Acute leukemia is a rapidly progressing disease that produces cells that are not fully developed. These immature cells cannot perform their normal functions. Chronic leukemia, however, usually progresses slowly, and patients have greater numbers of mature cells. In general, these more mature cells can carry out some of their normal functions. See *Normal Blood and Bone Marrow* on page 43.

Leukemia is further classified by the type of blood cell that becomes cancerous. Normal bone marrow cells form red blood cells, platelets and white blood cells. One type of white blood cell is called "myeloid," and another "lymphoid." The name of each of the four types of leukemia describes how quickly (acute) or slowly (chronic) the disease progresses, and identifies the type of white blood cell that is involved (myeloid or lymphoid).

What is CML?

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

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

CML is classified by the World Health Organization (WHO) as a "myeloproliferative neoplasm." This is a type of disease in which the bone marrow makes too many red blood cells, white blood cells or platelets. Patients with this

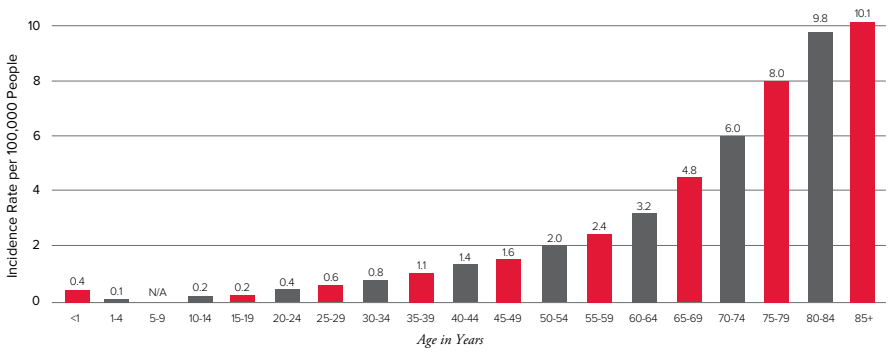
type of disease usually get worse slowly over time, as the number of extra cells build up in the blood and/or bone marrow. This may cause anemia, fatigue, infection, bleeding and other problems.

Easy-to-read information about CML can be found in the free booklet *The CML Guide: Information for Patients and Caregivers.*

Incidence. CML is a relatively rare disease. From 2009-2013 the incidence of CML was 1.8 per 100,000 men and women. CML is slightly more common in men than it is in women, and most cases of CML occur in adults. From 2009 to 2013, the median age at diagnosis for CML was 64 years. A small number of children develop CML. See *Children and Young Adults with CML* on page 38.

As shown in Figure 1 below, the frequency of CML increases with age. At age 65, the frequency is 4.8 in 100,000 people and increases to 10.1 in 100,000 people at 85 years and older. In coming years, the incidence of CML may increase, as a sizable portion of the US population is made up of people born between 1946 and 1964. These individuals have either reached, or are approaching, the age range associated with increased CML incidence.

Figure 1. Chronic Myeloid Leukemia: Age-Specific Incidence Rates 2009-2013



The horizontal axis shows five-year age intervals. The vertical axis shows the frequency of new cases of CML per 100,000 people, by age-group. (Source: Howlader N, Noone AM, Krapcho M, et al eds. SEER Cancer Statistics Review, 1975-2013. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. Accessed January 16, 2017.)

Causes. No one is born with CML. It is not passed from parent to child. It happens when there is an injury to the DNA of a single bone marrow cell. The mutated cell multiplies uncontrollably and crowds out the healthy red blood cells, white blood cells and platelets in the bone marrow. The CML cells then overflow into the bloodstream. Since CML is a slow-growing 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 leukemia, and often patients do not have any symptoms when diagnosed.

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

- Gender—CML is slightly more common in males than females.
- Age—The risk of getting 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. Most people treated for cancer with radiation do not develop CML, and most people who have CML have not been exposed to high doses of radiation. Exposures to diagnostic dental or medical x-rays have not been associated with an increased risk of CML.

The Philadelphia Chromosome and the *BCR-ABL* 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 pair looks different from the others and is identified by a number. There are a total of 46 chromosomes. Chromosome pairs are made up of one chromosome from each parent. Twenty-two of these pairs are called "autosomes," and they look the same in both males and females. The 23rd pair is the sex chromosomes, which are different for males and females. The pair in males is made up of one X chromosome and one Y chromosome, while the pair in females is made up of two X chromosomes.

Cells in the body have to make new copies of themselves to replace worn-out cells. To make a new copy of itself, a cell duplicates all of its contents including its chromosomes and then splits to form two identical cells. Sometimes the cell makes a mistake, either when it copies itself or when it divides into new cells. One type of mistake is called a "translocation." A translocation occurs when a piece of one chromosome breaks off and attaches to another chromosome. Sometimes pieces from two different chromosomes will trade places with each other. This can result in a "fusion gene," an abnormal gene that is formed when two different genes are fused together.

All cases of CML are caused by the *BCR-ABL* fusion gene. This gene is not found in normal blood cells. The *BCR-ABL* gene is formed by a translocation between parts of chromosomes 9 and 22 in a single bone marrow cell during cell division. Part of chromosome 9 attaches to chromosome 22, and part of chromosome 22 attaches to chromosome 9, resulting in a longer-than-normal chromosome 9 and a shorter-than-normal chromosome 22. The new abnormal

chromosome 22 is known as the "Philadelphia chromosome" (so called because it was discovered at the Winstar Institute in Philadelphia). "Ph" is the abbreviation for the Philadelphia chromosome. The Ph abbreviation with a "plus" sign (+) indicates that a person has the abnormal Ph chromosome. A Ph abbreviation with a "negative" sign indicates that a person does not have the Ph chromosome (see Figure 2 on page 10).

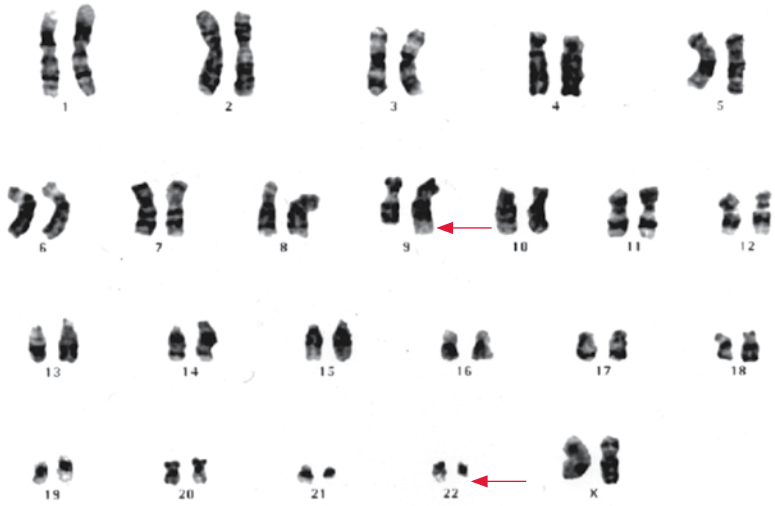
The short bottom piece of chromosome 9 has the *ABL* gene (named for Herbert Abelson, the scientist who discovered this gene). The break on chromosome 22 involves a gene called *"BCR"* (for breakpoint cluster region). The mutated *ABL* gene moves to chromosome 22 and fuses with the remaining portion of the *BCR* gene. The result of this fusion is the leukemia-causing gene *BCR-ABL* (see Figure 3 on page 11).

Genes provide cells with instructions for making proteins. The *ABL* gene instructs the cell to make a protein called a "tyrosine kinase." This protein sends signals that tell cells when to grow and divide. The abnormal *BCR-ABL* gene produces an abnormal protein called "BCR-ABL tyrosine kinase." This abnormal protein signals blood stem cells to produce too many granulocytes (white blood cells). These particular granulocytes have the *BCR-ABL* gene and are called "leukemia cells" or "CML cells." These granulocytes are not normal and do not become healthy white blood cells. They make new cells too quickly, and they do not die when they should. Eventually, granulocytes build up in the bone marrow and crowd out healthy red blood cells, white blood cells and platelets. When this occurs, anemia, infection or excessive bleeding may happen.

More than 95 percent of CML patients have the Philadelphia chromosome. These patients have Ph+ CML. A very small number of CML patients, however, have the *BCR-ABL* gene but the Philadelphia chromosome is undetectable. This is Ph-negative (Ph-) CML. Ph- CML patients who have the *BCR-ABL* gene rearrangement have the same prognosis as Ph+ patients.

Some patients have a type of leukemia in which too many granulocytes are made in the bone marrow. These patients, however, are Ph- and do not have the *BCR-ABL* gene. They may be diagnosed as having "atypical CML." They may have other unknown oncogenes causing their disease. These patients generally have poorer responses to treatment and shorter survival times.

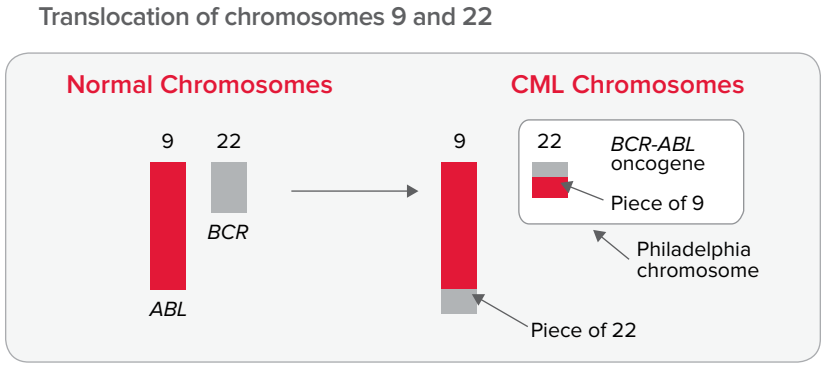
Figure 2. Marrow Cell Chromosomes



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 3. Chronic Myeloid Leukemia-Causing Event—How the *BCR-ABL* Cancer-Causing Gene (Oncogene) Is Formed



- A portion of the *ABL* gene from chromosome 9 translocates and fuses with the remaining portion of the *BCR* gene on chromosome 22. The translocated piece of chromosome 9 results in a fusion gene called *BCR-ABL*.
- The *BCR-ABL* fusion gene directs the production of an abnormal (mutant) protein, an enzyme called BCR-ABL tyrosine kinase (see Figure 4 on page 14).
- The abnormal enzyme protein is the principal factor in converting the marrow stem cell from a normal cell into a leukemic cell.

Signs and Symptoms

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

- 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 signs and symptoms of CML occur because the CML cells crowd out the bone marrow's healthy red blood cells, white blood cells and platelets. Anemia is a shortage of red blood cells that can cause weakness, fatigue and shortness of breath. A shortage of normal white blood cells can increase a CML patient's risk of infection, and a shortage of platelets can lead to excessive bruising or bleeding. Symptoms may also occur because CML cells collect in organs such as the spleen.

Diagnosis

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

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

The following are some tests that are done to diagnose CML.

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

- An increased white blood cell count, often to very high levels
- A decreased red blood cell count
- A possible increase or decrease in the number of platelets, depending on the severity of the person's CML.

Peripheral Blood Smear. Blood cells are stained (dyed) and examined with a light microscope. These samples show

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

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

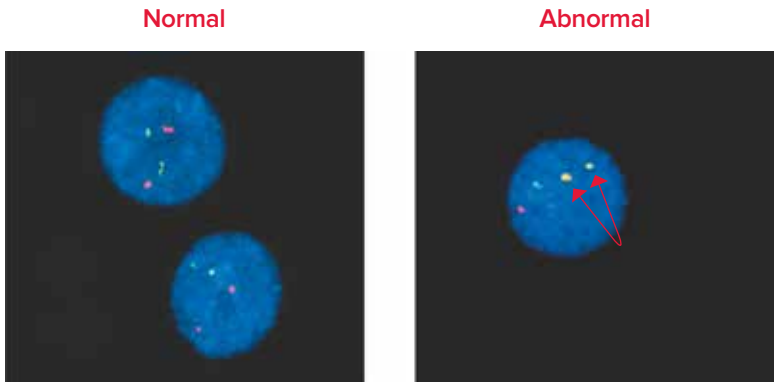
Blast cells are normally not present in the blood of healthy individuals.

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

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

FISH (Fluorescence In Situ Hybridization). FISH is a laboratory test used to examine genes and chromosomes in cells. FISH is a more sensitive method for detecting CML than the standard cytogenetic tests that identify the Ph chromosome. FISH can identify the presence of the *BCR-ABL* gene (see Figure 4 on page 14). Genes are made up of DNA segments. FISH uses color probes that bind to DNA to locate the *BCR* and *ABL* genes in chromosomes. Both *BCR* and *ABL* genes are labeled with different chemicals, each of which releases a different color. The color shows up on the chromosome that contains the gene—normally chromosome 9 for *ABL* and chromosome 22 for *BCR*—so FISH can detect the piece of chromosome 9 that has moved to chromosome 22 in CML cells. The *BCR-ABL* fusion gene is shown by the overlapping colors of the two probes.

Figure 4. Identifying the *BCR-ABL* Gene Using FISH



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

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

Blood cell counts, bone marrow examinations, FISH and qPCR may also be used to track a person's response to therapy once treatment has begun. qPCR testing is recommended every 3 months for 2 years as long as the patient's CML is responding to treatment. After 2 years, the test should be done every 3 to 6 months.

For more information about lab tests, see the free LLS booklet *Understanding Lab and Imaging Tests.*

Phases of CML

For most types of cancers, 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 will take the patient's CML stage into account when making a prognosis and planning treatment. CML, however, is not staged in the same way as most cancers. There are three groups, called "phases," of CML. Knowing a patient's CML phase helps doctors determine appropriate treatment and predict a patient's prognosis. The three phases of CML are

- Chronic phase
- Accelerated phase
- Blast phase (also called "blast crisis phase").

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

Chronic Phase. Most patients are diagnosed with chronic phase CML.

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 (i.e., symptoms go away, white blood cell counts return to normal levels, hemoglobin concentration improves and spleen reduces in size).

If untreated, chronic phase CML will eventually progress to accelerated phase CML.

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

People with accelerated phase CML may have

- More than 20 percent basophils (type of white blood cell) in the bloodstream
- High white blood cell counts
- Very high or very low platelet counts
- Increasing spleen size
- Anemia
- Additional chromosome abnormalities
- New chromosome changes (mutations) in the CML cells.

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

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

People who have blast phase CML may have

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

Prognostic Factors. Along with the phases of CML, there are other factors that affect treatment decisions and predict a patient's prognosis (chance for recovery). These are known as "prognostic factors." The following are prognostic factors for patients with CML at the time of diagnosis:

- Phase of CML—Patients who have either accelerated or blast phase CML have a less favorable prognosis than those who have chronic phase CML.
- Age—Patients 60 years of age or older have a less favorable prognosis.
- Spleen size—A patient with an enlarged spleen has a less favorable prognosis.
- Platelet count—Patients who have very high or very low platelet counts have a less favorable prognosis.
- Blasts in the blood—Patients who have a high number of blasts in the blood have a less favorable prognosis.

- Increased numbers of basophils and eosinophils in the blood—Patients with an increase in these types of white blood cells have a less favorable prognosis.

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

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

See the section entitled *More Information* on page 53 for links to these scoring systems.

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

Treatment

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

CML does not appear to be curable with current drug therapies. But over time, more and more CML patients are achieving extremely deep remissions. With current drug therapies, most people diagnosed with chronic phase CML can expect to live good-quality lives for many years.

The treatment of CML has improved significantly since the introduction of the tyrosine kinase inhibitor (TKI), imatinib mesylate (Gleevec®) in 2001, and the approval of second-generation TKIs, dasatinib (Sprycel®) in 2006 and nilotinib (Tasigna®) in 2007. The introduction of TKIs changed CML from a potentially fatal disorder to one that can be controlled. Not all patients, however, respond to TKIs, and it is possible that patients will develop resistance to these drugs.

The approach for treating each patient is based on the phase of CML at diagnosis, risk scores, age, and the patient's other health issues. For a list of drugs used to treat CML, see Table 1 on page 26.

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

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

Leukapheresis is a procedure that uses a machine similar to a dialysis machine to remove white blood cells from the circulating blood. Leukapheresis is used to lower WBC counts if chronic phase CML is diagnosed during the first months of pregnancy, when other treatments may be harmful to fetal development. For more information about pregnancy and CML, see page 39.

Tyrosine Kinase Inhibitor Therapy. Tyrosine kinase inhibitors (TKIs) are a type of targeted therapy. TKIs come as pills, taken orally. A targeted therapy identifies and attacks specific types of cancer cells while causing less damage to normal cells. In CML, TKIs target the abnormal BCR-ABL protein that causes uncontrolled CML cell growth and block its function, causing the CML cells to die.

Three TKI drugs are approved as initial therapy (first-line treatment) for chronic phase CML. These drugs are

- Imatinib mesylate (Gleevec®)
- Dasatinib (Sprycel®)
- Nilotinib (Tasigna®).

"Initial" treatment is the first therapy given for a disease. If the first treatment does not work because of intolerance (intolerable side effects) to a particular drug or drug resistance (CML is not responding to the drug) during therapy, a second treatment option is tried. If both the initial treatment and the subsequent treatment (second-line) fail to work, a third treatment option (third-line treatment) can be offered to the patient.

In the case of resistance to and/or intolerance to second-line treatments, other TKI options for treatment include

- Bosutinib (Bosulif®)
- Ponatinib (Iclusig®).

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

Imatinib mesylate (Gleevec)

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

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

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

Dasatinib (Sprycel)

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

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

Nilotinib (Tasigna)

- Nilotinib is a second-generation TKI approved by the FDA in 2007 to treat CML and is approved for
  - Newly diagnosed adults with Ph+ CML in chronic phase
  - Ph+ CML adults in chronic phase and accelerated phase who are either resistant to or intolerant to prior therapy including imatinib.
- Grapefruit products increase the amount of nilotinib in the body. This may increase a patient's chance for serious and life-threatening side effects. Patients should avoid grapefruit, grapefruit juice and any supplement containing grapefruit extract while taking nilotinib.
- Nilotinib is usually taken twice a day. It should be taken on an empty stomach. Patients should avoid eating food for at least 2 hours before the dose is taken and also for at least 1 hour after the dose is taken.
- Studies of nilotinib have shown that it is more potent than imatinib and that it induces faster and deeper molecular responses than the responses from imatinib. To date, nilotinib has not been shown to increase survival versus 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 medicines, including over-the-counter medicines, that they are taking.
- Patients who need to take antacids (medicines to treat heartburn) should not take them at the same time as nilotinib. Patients who take H2 blockers (histamine type 2 receptor antagonists/blockers) should take these medicines about 10 hours before taking nilotinib or 2 hours after taking nilotinib. Patients taking antacids containing aluminum hydroxide, magnesium hydroxide or

simethicone should take these medicines about 2 hours before or about 2 hours after taking nilotinib.

- Common side effects include
  - Nausea, vomiting, diarrhea
  - Rash
  - Headache
  - Fatigue
  - Itching
  - Cough
  - Constipation
  - Muscle and joint pain
  - Runny or stuffy nose, sneezing, sore throat
  - Fever
  - Night sweats
- Serious side effects of nilotinib include
  - Low blood cell counts. Low numbers of red blood cells, white blood cells and platelets can put a patient at increased risk for anemia, infection and/or bleeding.
  - QT interval prolongation, a serious heart problem that causes a change in heartbeat rhythm. This condition can be fatal, and patients should contact their doctor immediately if they feel lightheaded, faint or have an irregular heartbeat while taking nilotinib. Before starting nilotinib and during treatment with nilotinib, doctors should check patients' hearts with a test called an "electrocardiogram" (ECG).
  - Decreased blood flow to the leg, heart or brain
  - Liver damage-symptoms, including yellow skin and eyes
  - Inflammation of the pancreas. Symptoms include stomach pain with nausea and vomiting.
  - Hyperglycemia, a higher than normal amount of glucose (sugar) in the blood
  - Fluid retention. Symptoms include shortness of breath, rapid weight gain and swelling.

Bosutinib (Bosulif)

- Bosutinib is a second-generation TKI that was approved by the FDA in 2012. It is approved to treat adults with chronic, accelerated or blast phase CML with

resistance to or intolerance to prior therapy. The drug is only approved to treat CML in patients after another TKI has stopped working or has caused very bad side effects.

- Side effects include
  - Stomach pain, diarrhea, nausea and vomiting
  - Fluid retention
  - Rash
  - Fatigue
- Serious side effects include
  - Low blood cell counts. Low numbers of red blood cells, white blood cells and platelets can put a patient at increased 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 approved for
  - Adult patients in chronic, accelerated or blast phase CML for whom no other TKI is indicated
  - Adult patients with the *T315I* mutation in chronic, accelerated or blast phase CML
- Ponatinib may be taken either with or without food.
- Ponatinib targets all of the changes (mutations) on the BCR-ABL protein that are resistant to imatinib and other TKIs. This drug, however, can cause severe side effects and is not a good option for all patients.
- Most common side effects include
  - Skin rash
  - Stomach-area (abdomen) pain
  - Fatigue
  - Headache
  - Dry skin
  - Fever

- Constipation
- High blood pressure

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

TKI Resistance. A "treatment response" is the term used to describe an improvement (caused by treatment) in a disease. "Drug resistance" is the term used to describe the reason that a disease has not responded to treatment. Drug resistance in CML occurs when cancer cells do not respond to a drug that is being used to kill or weaken them. "Primary resistance" is the term that describes resistance to a drug that is being taken for the first time in the disease process. This type of resistance is rare in CML patients. The most common type of drug resistance in CML patients occurs when cancer cells initially respond to a treatment but then stop responding. This response is called "secondary resistance." In CML, it is often caused by mutations in the *BCR-ABL* gene. These mutations alter the shape of the BCR-ABL protein which can affect the blocking action of the TKI on *BCR-ABL,* allowing cancer cells to grow again. Sometimes resistance to a TKI can be stopped by increasing the dose of the drug

or by switching to another type of TKI. Second-generation TKIs can be effective in treating patients with mutations that are resistant to imatinib. *BCR-ABL* gene mutation analysis is a test that identifies the mutations in the *BCR-ABL* gene that are responsible for TKI resistance. This information can help a doctor decide which drug to prescribe.

Drug Interactions. Certain drugs, herbal supplements and even foods can affect the way TKIs work in the body. Corticosteroids, anti-seizure medication, antacids, and the herbal supplement St. John's Wort can make some TKIs less effective. On the other hand, certain antibiotics and antifungal medication and grapefruit products may increase the levels of TKIs in the blood to high, unsafe levels.

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 that they are taking to be certain that it is safe to take the products with their TKIs. And it is important to ask the doctor about any foods that should be avoided.

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

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

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

Patients must take their medication as prescribed to get the best response. Poor adherence to the medication regimen is the main reason for inadequate response to the prescribed treatment. Patients should not stop taking their medication, nor should they take less than the amount prescribed, unless they are following their doctors' instructions. Taking less than the amount prescribed can affect how well the medication works and may result in unfavorable treatment outcomes.

Table 1. Drugs Used to Treat CML

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

The following drugs were used as initial therapy before TKIs were introduced. They may continue to be used in select patients.

Interferon alfa (Roferon-A®, Intron A®)
Pegylated interferon alfa
Hydroxyurea (Hydrea®)
Cytarabine (Cytosar-U®)
Busulfan (Myleran®)

Chemotherapy. Chemotherapy is generally used only in patients with blast phase disease as a way to get the CML back into chronic phase. Very high-dose chemotherapy is sometimes used in the protocol that prepares patients for an allogeneic stem cell transplantation.

Omacetaxine mepesuccinate (Synribo®), a chemotherapy drug, is a treatment option for adults with chronic or accelerated phase CML with resistance to and/or intolerance to two or more TKIs. Omacetaxine can be used to treat all mutations resistant to TKIs including the *T315I* mutation. In general, its use is limited to patients who have exhausted all other TKI options and who are not candidates for allogeneic transplant.

Omacetaxine is given as a liquid that is injected under the skin. The most common side effects include

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

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

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

Interferon can cause significant side effects including

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

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

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

Allogeneic Stem Cell Transplantation. Allogeneic stem cell transplantation (infusion of donor stem cells into a patient) is the best-documented curative treatment for select patients with CML at this time. This type of transplant, however, can cause serious or even life-threatening complications and side effects, and it is often not a good option for older patients or for patients who have other health problems. Results for matched sibling and matched unrelated donors are very similar.

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

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

The most important prognostic factor for survival post-transplant is the phase of CML. Approximately 90 percent of patients with chronic phase CML will be disease-free for 5 years. 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.

For more information about all types of stem cell transplantation, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation.*

Treating CML by Phase

Each phase of CML requires different treatment.

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

- Imatinib 400 mg once a day
- Dasatinib 100 mg once a day
- Nilotinib 300 mg twice a day

When choosing a first-line TKI, doctors may consider such factors as a patient's pre-existing health conditions, age, risk score, dose schedule and cost.

After the start of therapy, doctors will monitor patients to determine how well a patient is responding to treatment. A patient who is responding well will stay on his or her current drug therapy. If the patient is not meeting treatment milestones, the doctor will need to find out why. A gene mutation analysis should be done to check for mutations of the *BCR-ABL* gene. The doctor will also determine whether or not the patient has been adhering to the treatment plan. If the patient's current treatment is not working, there are several options. They include

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

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

In accelerated phase CML, the cancer cells often acquire new genetic mutations that may make treatments less effective. Patients should undergo *BCR-ABL* gene mutation analysis before starting treatment to determine which treatment option is best for them.

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

- Imatinib 600 mg once a day
- Dasatinib 140 mg once a day
- Nilotinib 400 mg twice daily
- Bosutinib 500 mg once daily

If the CML progressed from chronic phase to accelerated phase during TKI therapy, a patient can try to increase the dosage of the current TKI (if possible) or take another TKI that the patient has not tried before. Other options include

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

Another option for patients with accelerated phase CML is to receive treatment within a clinical trial. A clinical trial is a study done by doctors to test new drugs or 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, improve quality of life and to find a cure. Patients should discuss the potential benefits and risks of participating in a clinical trial with their doctors.

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

Two important tests are needed before starting treatment for blast phase CML. The first test determines whether the blast phase involves myeloid or lymphoid blast cells. This test is needed because the type of blast cells is a factor in the treatment decision. The second test, a *BCR-ABL* gene mutation analysis, checks for mutations in the part of the *BCR-ABL* gene that makes the BCR-ABL protein. Different mutations can make the BCR-ABL protein either more or less resistant to certain TKIs.

One option for patients with blast phase CML is to receive treatment within a clinical trial. Patients should discuss the potential benefits and risks of participating in a clinical trial with their doctors.

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

Measuring Treatment Response

After patients begin treatment, their doctors will periodically order blood and bone marrow tests to determine whether they are responding to treatment. A treatment response is an improvement related to the patient's treatment. Monitoring treatment response is one of the key strategies for managing CML. In general, the greater the response to drug therapy, the longer the disease will be controlled. Table 2 on page 34 shows the different types of treatment responses for CML.

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

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

- A partial hematologic response—The numbers of each type of blood cells begin to return to a normal level.
- A complete hematologic response (CHR)—The blood counts have returned to normal. Most patients on TKI therapy will have a complete hematologic response within 3 months of beginning treatment.

Cytogenetic Response. This is a measurement of the number of cells in the bone marrow that contain the Ph chromosome. Either cytogenetic testing or FISH is used to measure this.

- Complete cytogenetic response (CCyR)—No cells with the Ph chromosome can be detected in the bone marrow
- Partial cytogenetic response (PCyR)—Tthe Ph chromosome is found in 1 to 35 percent of bone marrow cells
- Major cytogenetic response (MCyR)—0 to 35 percent of the cells have the Ph chromosome. This term is occasionally used to describe a complete or partial cytogenetic response
- Minor cytogenetic response—The Ph chromosome is found in more than 35 percent of cells in the bone marrow

Bone marrow cytogenetics are tested at the 3-month and 6-month follow-up visits to check the patient's response to therapy if qPCR is not available (See *Quantitative Polymerase Chain Reaction* on page 14).

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

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

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

- 1-log reduction indicates that the *BCR-ABL* levels have decreased to 10 times below the standardized baseline. This means that 10 percent of cells (10 out of every 100 cells) have the *BCR-ABL* gene. This is also written as "*BCR-ABL* 10 percent." This reduction is equivalent to an early molecular response.
- 2-log reduction means that *BCR-ABL* levels have decreased to 100 times below the standardized baseline. This means that 1 percent of cells (1 out of every 100 cells) have the *BCR-ABL* gene. This is also written as "*BCR-ABL* 1 percent."
- 3-log reduction indicates that the *BCR-ABL* levels have decreased to 1,000 times below the standardized baseline. This means that 0.1 percent of cells (1 out of every 1,000 cells) have the *BCR-ABL* gene. This is written as "*BCR-ABL* 0.1%." It is also known as a "major molecular response" (MMR).
- 4.5-log reduction is referred to as a "complete molecular response" (CMR) or a "deep molecular response." Doctors may refer to this as "MR4.5." A 4.5-log reduction indicates that 0.0032% of cells (1 out of every 32,000 cells) have the *BCR-ABL* gene. Achieving a deep molecular response is a sign of disease remission. Patients who achieve and then sustain a deep molecular response for a

significant period of time may be considered candidates for discontinuing drug therapy in a clinical trial. See *Research and Clinical Trials* on page 40.

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

qPCR testing is recommended every 3 months for 2 years as long as the patient's CML is responding to treatment. After 2 years, the test should be done every 3 to 6 months.

BCR-ABL Gene Mutation Analysis

Sometimes mutations occur in the part of the *BCR-ABL* gene that makes the BCR-ABL protein. These mutations alter the shape of the BCR-ABL protein, and this can affect how TKIs bind to the BCR-ABL protein to block the growth signals.

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

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

A mutation analysis test does not need to be done in a patient who is switching medication as a result of side effects.

Table 2. Chronic Myeloid Leukemia (CML) Treatment Responses

Type of Response		Features	Test Used to Measure Response
Hematologic	Complete hematologic response (CHR)	• Blood 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) chromosomes detected	Bone marrow cytogenetics or FISH
	Partial cytogenetic response (PCyR)	1% to 35% of cells have Ph chromosome	
	Major cytogenetic response (MCyR)	0% to 35% of cells have the Ph chromosome	
	Minor cytogenetic response	More than 35% of cells have the Ph chromosome	
Molecular	Complete molecular response (CMR)	No *BCR-ABL* gene detectable	Quantitative PCR (qPCR) using International Scale (IS)
	Major molecular response (MMR)	At least a 3-log reduction* in *BCR-ABL* levels or *BCR-ABL* 0.1%	

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

Source: *The NCCN Clinical Practice Guidelines in Oncology™ for Chronic Myelogenous Leukemia, 2016.*

For people who experience a loss of response to a TKI, or those who do not achieve the expected response within a given period of time (see Table 3 on pages 35-37), the most common options are switching to another approved TKI or participating in a clinical trial.

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

Time After Diagnosis	Optimal Response	Follow-up Recommendation Guidelines	
		If Milestone Is Achieved	**If Milestone Is Not Achieved**
3 months	*BCR-ABL* ≤10% by qPCR	• Continue treatment at same dosage • Monitor with quantitative PCR (qPCR) every 3 months	• Evaluate patient compliance • Perform *BCR-ABL* gene mutation testing **THEN** Increase tyrosine kinase inhibitor (TKI) dosage (if possible) **OR** Change to alternate TKI **OR** Enter clinical trial **OR** Evaluate for hematopoietic stem cell transplantation (HSCT)
	Partial cytogenetic response (PCyR)		
	Complete hematologic response (CHR)		
6 months	*BCR-ABL* ≤10% by qPCR	• Continue treatment at same dosage • Monitor with qPCR every 3 months	• Evaluate patient compliance • Perform *BCR-ABL* gene mutation testing **THEN** Increase TKI dosage (if possible) **OR** Change to alternate TKI **OR** Enter clinical trial **OR** Evaluate for HSCT
	Partial cytogenetic response (PCyR) or better		
	Continued complete hematologic response (CHR)		

Table 3 (continued). CML Treatment Response Milestones and Follow-up Recommendation Guidelines

Time After Diagnosis	Optimal Response	Follow-up Recommendation Guidelines	
		If Milestone Is Achieved	**If Milestone Is Not Achieved**
12 months	Complete cytogenetic response (CCyR)	• Continue treatment at same dosage • After CCyR is achieved, monitor with qPCR every 3 months for 2 years and every 3-6 months thereafter	• Evaluate patient compliance • Perform *BCR-ABL* gene mutation testing **THEN** Increase TKI dosage (if possible) **OR** Change to alternate TKI or omacetaxine **OR** Enter clinical trial **OR** Evaluate for HSCT
18 months	Major molecular response (MMR)	• Continue treatment at same dosage • Continue monitoring with qPCR every 3-6 months or as indicated by doctor	• Evaluate patient compliance • Perform gene mutation *BCR-ABL* testing **THEN** Change to alternate TKI and repeat bone marrow evaluation after 3 months **AND** Evaluate for HSCT **OR** Enter clinical trial

Table 3 (continued). CML Treatment Response Milestones and Follow-up Recommendation Guidelines

Time After Diagnosis	Optimal Response	Follow-up Recommendation Guidelines	
		If Milestone Is Achieved	If Milestone Is Not Achieved
18 months and beyond	Stable or improving major molecular response (MMR)	Continue treatment and follow-up care as indicated by doctor	• Evaluate patient compliance • Perform *BCR-ABL* gene mutation testing **THEN** Change to alternate TKI and repeat bone marrow evaluation and qPCR as indicated **AND** Evaluate for HSCT **OR** Enter clinical trial

The optimal milestones for the first 18 months of CML treatment and general follow-up guidelines are listed in this table. The inability to achieve a milestone at a certain time after the start of therapy may indicate a need to change the direction of treatment. Follow-up recommendations are based on the individual patient's response to treatment. Talk to your doctor about your milestones and if you have reached an appropriate response.
Source: *The NCCN Clinical Practice Guidelines in Oncology™ for Chronic Myelogenous Leukemia, 2016.*

Every patient responds differently to CML drug therapy. These general guidelines for CML drug therapy are available online through the National Comprehensive Cancer Network (NCCN) and the European Leukemia Net (ELN) (see the section entitled *More Information* on page 53 for links to these scoring systems). An individual's CML drug therapy response is measured against his or her own results at the start of therapy, called "baseline" results. Thus, if a person has a high white blood cell count at the beginning of therapy, a "complete hematologic response and some cytogenetic improvement" may occur longer than 3 months after starting therapy. A complete molecular response is optimal, but only some patients attain this. Even without a complete molecular response, CML may be well controlled by drug therapy.

Children and Young Adults with CML

A small percentage of patients diagnosed with CML are children and young adults. CML represents about 3 percent of newly diagnosed childhood leukemias. Because CML is rare in children, there have only been a few pediatric studies evaluating the use of TKI therapy in children. Consequently, 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. Children with CML should be treated by doctors who specialize in treating children with blood cancers.

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 for 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. Since children with CML may receive TKI therapy for much longer than adults and during periods of active growth, follow-up care is very important. In addition to testing their pediatric patients' responses to therapy, doctors should also monitor children's

- 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 important to follow the doctor's directions and keep taking the medication for as long as prescribed. Nonadherence to TKI treatment has the potential of suboptimal response or even treatment failure.

Taking into account the potential concerns of lifelong TKI treatment, researchers are studying stopping TKIs after a period of deep molecular response. At this time, there is limited information on the long-term outcomes of patients with CML after they have stopped taking imatinib. Intermittent TKI dosing is another potential approach to reducing long-term side effects in pediatric CML patients, but more studies are needed to evaluate this approach. Allogeneic stem cell transplantation is another treatment option. Because there have been no randomized controlled trials comparing stem cell transplantation and imatinib in children due to the small number of pediatric patients, the decision on how to

treat CML has been individualized. Stem cell transplantation should be evaluated against the complications associated with lifelong TKI use.

Talk to your child's doctor about the best treatment for your child and discuss 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. See the free LLS booklets *Choosing a Blood Cancer Specialist or Treatment Center Facts* and *Coping with Childhood Leukemia and Lymphoma* for more information.

Fertility, Pregnancy and TKIs

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

Growing numbers of CML patients of childbearing age are living with stable remissions and are considering having children while taking TKIs. In some men taking TKIs, researchers have observed low sperm counts and poor sperm motility. Male patients should consider having a fertility evaluation before conceiving a baby. And, prior to treatment, men may want to consider cryopreservation (sperm banking). Depending on the TKI, their doctor may recommend discontinuing treatment 3 to 4 weeks prior to a planned conception. Children born to men taking imatinib at the time of conception are not at risk of passing on Ph abnormalities to their children.

For female patients who want to become pregnant, the issues are more complex and there is limited data. Imatinib, dasatinib and nilotinib are known to cause embryonic or fetal toxicities in animal studies. In some instances, female patients receiving TKI therapy at the time of conception have had miscarriages or babies born with congenital abnormalities. A patient should consult with her hematologist-oncologist as well as a high-risk obstetrician to discuss the potential risks of discontinuing TKI therapy during pregnancy versus the potential risks to the fetus of continuing TKI therapy.

One option is to discontinue TKI therapy during pregnancy. Doctors may advise planning a pregnancy when the patient's response to therapy is as deep as possible, at least a major molecular response. The patient would stop therapy prior to conception and during the pregnancy. The patient would then resume TKI therapy immediately after the birth of her child. During pregnancy a patient's blood should be closely monitored for signs of disease progression. This option should only be done under the close observation of a hematologist-oncologist and a high-risk obstetrician.

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

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

Research and Clinical Trials

CML patients are encouraged to explore clinical trials. Clinical trials test new drugs and treatments, many of which are being supported by LLS research programs, before they are approved by the FDA as standard treatments.

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

Clinical trials are designed to be accurate and very safe. There are clinical trials for newly diagnosed patients, for patients with advanced disease, and for patients who are either intolerant to or resistant to their current medications. Sometimes, a clinical trial is the best option for a patient. Clinical trials hold great promise to increase remission rates and find a cure for CML.

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. Our Information Specialists can search for clinical trials on behalf of patients, family members and healthcare professionals. When appropriate, personalized clinical-trial navigation by trained nurses is available.

Research Approaches. Current goals of CML research are to

- Develop truly curative therapies
- Develop therapies that can work when others have failed
- Decrease the side effects of treatment

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

Improving Current Treatments. Despite the great results of TKI therapy in chronic phase CML, many trials are looking at further optimization. Research includes

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

New Drug Therapies. TKIs treat CML by targeting the BCR-ABL protein that directs the growth of the leukemia cells. It is not uncommon, however, for CML not to respond, to respond partially, or to become resistant to these drugs. ABL001 is an investigational drug designed to deactivate the BCR-ABL protein. Currently, TKI treatments target the BCR-ABL protein, but ABL001 targets a different location on the protein. Researchers are also studying the drug rebastinib. Rebastinib is a new TKI that is also designed to overcome imatinib resistance by binding to a different location on the BCR-ABL protein. Rebastinib may work against resistant mutations including the *T315I* mutation.

Disease Eradication Strategies. Even after it seems as though CML has been successfully treated, a very small number of leukemia stem cells may remain in the patient's blood and marrow. This condition is referred to as "minimal residual disease" (MRD). These stem cells appear to be resistant to TKI therapy. This has led to strategies aimed at targeting the stem cell signaling pathways that are involved in the cells' survival. Researchers are trying to obtain a better understanding of the mechanisms leading to CML leukemic stem cell survival. One area of research involves inhibitors of a protein called "smoothened" (SMO). The inhibitors are expected to target the SMO protein found on CML stem cells while sparing normal blood stem cells. A number of additional pathways are being studied, and there are ongoing efforts to assess their importance in CML patients.

TKI Discontinuation Studies. Treatment of CML with TKIs has advanced to a point where many patients achieve either very low or undetectable levels of the *BCR-ABL* gene in their blood. Researchers are studying whether some patients with deep and sustained molecular responses can safely discontinue TKI treatment and experience a treatment-free remission.

In one clinical trial, approximately 40 percent of CML patients who had achieved a complete molecular remission for at least 2 years were able to stop their TKI

therapy without relapsing. Further, those who did relapse were able to restore remissions by resuming their TKI therapy. Additional research is still needed to establish criteria for safely ending TKI therapy. At this time, discontinuing TKI therapy should only be done within the confines of a clinical trial.

Vaccine Therapy. Various forms of vaccine therapy are being studied to see whether they can reduce or eliminate residual leukemia cells in CML patients. TKIs destroy most leukemic cells in the body, but in most patients, some of the cancerous cells remain. These remaining cells can cause a relapse, especially if the TKI therapy is stopped. Researchers are trying to find ways to help the immune system recognize the difference between normal cells and CML cells so the immune system can attack the cancer cells remaining after TKI therapy. See the free LLS booklet *Immunotherapy Facts* for information about the development of blood cancer vaccines.

Reduced-Intensity Stem Cell Transplantation. A modified form of allogeneic transplantation known as "reduced-intensity" or "nonmyeloablative" allogeneic stem cell transplantation may be an option for CML patients who do not respond to other treatments. Patients being prepared for a reduced-intensity transplant receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant, compared to the doses given to patients receiving an allogeneic transplant. Immunosuppressive drugs are used to prevent rejection of the donor stem cells. The engraftment of donor immune cells may allow these cells to attack the patient's CML cells (a result called "graft-versus-tumor effect"). The theory being tested with a reduced-intensity transplant is that by undergoing less toxic procedures prior to the transplant, the body is better able to withstand the transplant. However, full donor engraftment would still take place, and the desired graft-versus-leukemia effect would still occur.

Other drugs are being tested in clinical trials to enhance the graft-versus-leukemia effect of stem cell transplantation and to reduce the risks of graft-versus-host disease.

In addition, research is underway evaluating the use of umbilical cord blood as a source of stem cells for transplantation in children and adults. Cord blood provides another potential source of matched, unrelated stem cells for patients who do not have a matched, related stem cell donor. Results from cord-blood stem cell transplants have been promising, and there appears to be a reduced risk of acute graft-versus-host disease in younger cord-blood transplant patients. For more information about all types of stem cell transplantation, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Follow-up Care

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

- Will need to see their doctor on a regular basis: the doctor will evaluate their health, blood cell counts, their molecular responses to treatment using qPCR tests and possibly 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 shingles vaccine, should not be administered. Your doctor can give you more information.
- Always need to keep good records and treatment notes. This information should include
  - Doctors' names and contact information
  - Medical history
  - CML diagnosis
  - Copies of all pathology reports
  - All treatments
  - Names of drugs taken
  - Transplant information
  - Any other important information

Normal Blood and Bone Marrow

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

Blood is composed of plasma and cells.

Plasma. 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 made by the liver
- Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
- Immunoglobulins, proteins that help the body fight infection

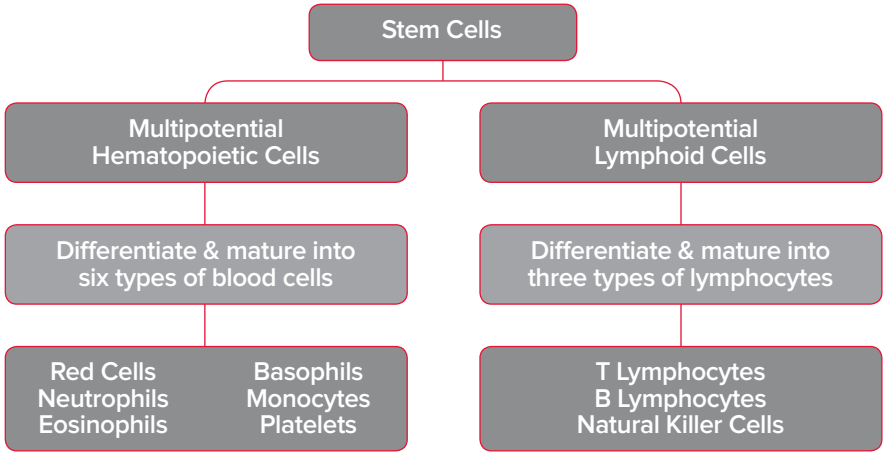
- Hormones, such as thyroid hormone and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B12
- Electrolytes, such as calcium, potassium and sodium

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

There are three types of blood cells. They are

- Red blood cells that carry oxygen and
  - Make up a little less than half of the body's total blood volume
  - Are filled with hemoglobin, a protein that picks up oxygen from the lungs and delivers it to the cells throughout the body. Hemoglobin then picks up carbon dioxide from the cells and delivers it to the lungs, where it is removed when a person exhales.
- Platelets
  - Are small cells (one-tenth the size of red blood cells)
  - Help stop bleeding from an injury. For example, when a person has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the blood vessel, clump together, and plug up the bleeding site with the help of blood-clotting proteins such as fibrin and electrolytes such as calcium.
- White blood cells (WBCs) that fight infections. There are several types of WBCs, including
  - Neutrophils and monocytes. These are "phagocytes" (eating cells) that eat and kill bacteria and fungi. Unlike the red blood cells and platelets, monocytes can leave the bloodstream and enter the tissue, where they can attack invading organisms and fight off infection.
  - Eosinophils and basophils. These white blood cells respond to allergens and parasites.
  - Lymphocytes. This type of white blood cell is mostly found in the lymph nodes, spleen and lymphatic channels. Lymphocytes are a key part of the immune system. There are three major types of lymphocytes
    - T lymphocytes (T cells)
    - B lymphocytes (B cells)
    - Natural killer (NK) cells

Figure 5. Blood Cell & Lymphocyte Development



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

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

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

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

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

Health Terms

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

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

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

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

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

BCR-ABL Tyrosine Kinase Inhibitor. See Tyrosine Kinase Inhibitor.

Blast Cell. A young (or immature) blood cell.

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

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

Bone Marrow Biopsy. A test to examine bone marrow cells to detect cell abnormalities. This test differs from a bone marrow aspiration in that a small amount of bone filled with marrow is removed, usually from the hip (pelvic)

bone. After medication is given to numb the skin, a special hollow biopsy needle is used to remove a piece of bone containing marrow. Bone marrow aspiration and bone marrow biopsy may be done in either the doctor's office or in a hospital. The two tests are almost always done together.

Bone Marrow Transplantation. See Allogeneic Stem Cell Transplantation.

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

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

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

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

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

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

Drug Intolerance. Unable to tolerate the side effects of the drug.

Drug Resistance. The drug isn't working effectively to combat the disease.

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

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

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

Graft-Versus-Host Disease (GVHD). A disease caused when transplanted donor stem cells (the graft) perceive the cells of the transplant recipient (the host) as foreign, and the transplanted cells attack the recipient's normal, healthy cells.

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

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

GVHD. See Graft-Versus-Host Disease.

Hasford Scoring System. A scoring system that estimates survival of patients with CML. The system designates patients as "low risk," "intermediate risk" or "high risk." Scores are based on the following diagnostic markers:

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

Hemapheresis. See Apheresis.

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

Hematologic. Of or relating to blood.

Hematologist. A doctor who specializes in blood cell diseases.

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

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

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

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

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

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

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

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

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

Monocyte/Macrophage. A monocyte is a type of white blood cell that is made in the bone marrow and travels through the bloodstream to tissues in the body where it becomes a macrophage. It represents about 5 to 10 percent of the cells in normal human blood. The macrophage is the monocyte-in-action: It can combat infection in the tissues, ingest dead cells (in this function it is called a "scavenger cell") and assist lymphocytes in their immune functions.

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

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

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

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

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

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

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

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

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

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

Philadelphia Chromosome (Ph Chromosome). An abnormality of chromosome 22 found in the bone marrow and blood cells of most patients with chronic myeloid leukemia and of some patients with acute lymphoblastic leukemia. It is formed when parts of chromosome 9 and 22 break off and trade places. The result is a chromosome 22 that is shorter than normal. The exchange of DNA between chromosomes 9 and 22 results in the creation of a new gene (an oncogene) called *"BCR-ABL"* on chromosome 22.

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

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

Quantitative Polymerase Chain Reaction (qPCR). A technique to expand trace amounts of DNA so that the specific type of the DNA can be studied. This technique has become useful in detecting a very low concentration of residual blood cancer cells, too few to be seen using a microscope. qPCR 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 (erythrocyte) 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.

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

Refractory. Disease that has not responded to initial treatment. Refractory disease may be disease that is getting worse or staying the same (stable disease).

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

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

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

Response to Treatment. An improvement related to treatment.

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

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

Stem Cell Transplantation. See Allogeneic Stem Cell Transplantation.

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

Thrombocyte. A platelet.

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.

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

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

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

More Information

Free LLS booklets include

Blood and Marrow Stem Cell Transplantation
Choosing a Blood Cancer Specialist or Treatment Center Facts
The CML Guide: Information for Patients and Caregivers
Understanding Clinical Trials for Blood Cancers
Understanding Lab and Imaging Tests
Understanding Side Effects of Drug Therapy

Visit "Suggested Reading" at www.LLS.org/suggestedreading to see helpful books on a wide range of topics.

The following Web sites provide information about diagnosis and treatment guidelines.

European LeukemiaNet

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

National Comprehensive Cancer Network

www.nccn.org/patients
Choose **NCCN Guidelines for Patients** on the top navigation bar.

The following Web sites provide information regarding the various scoring systems for CML.

European Treatment and Outcomes Study Score

www.leukemia-net.org
Choose **leukemias** in the top navigation bar, select **CML** on the left navigation bar and then choose **EUTOS Score** on the left navigation bar.

Sokal and Hasford (also known as "Euro") Scores

www.leukemia-net.org
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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Notes

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REACH OUT TO OUR **INFORMATION SPECIALISTS**

The Leukemia & Lymphoma Society's (LLS) Information Specialists provide patients, families and healthcare professionals with the latest information on leukemia, lymphoma and myeloma. Our team consists of master's level oncology social workers, nurses and health educators who are available by phone Monday through Friday, 9 am to 9 pm (ET).

Co-Pay Assistance
LLS's Co-Pay Assistance Program helps blood cancer patients cover the costs of private and public health insurance premiums, including Medicare and Medicaid, and co-pay obligations. Support for this program is based on the availability of funds by disease. **For more information, call 877.557.2672 or visit www.LLS.org/copay.**

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Our Mission:

Cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families.

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