someday is today

LEUKEMIA & LYMPHOMA SOCIETY®

fighting blood cancers

Chronic Myeloid Leukemia

Paula, CML survivor

This publication was supported by Bristol-Myers Squibb

Revised **2014**

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 almost 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 cancers.

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

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Acknowledgement

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

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Introduction

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

The National Cancer Institute estimates 33,990 people in the United States are living with CML, with another 5,980 new cases expected in 2014.[1]

Today, there is positive news for people with CML.

Since 2001, six new drugs have been approved for treatment and with new research, innovations in treatment and clinical trials, people are not only living longer with CML, but can often live with this type of leukemia as a manageable chronic condition.

At LLS, we know that the more you know about your disease, the better you can take care of yourself, your mind and body and your health.

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

We trust the information in this booklet provides a good working knowledge base and that it reinforces what you already know. We hope you keep this booklet handy and, should you ever feel alone confronting problems, we hope you will turn to it for information and guidance, locating the support and resources you need.

We are here to help.

[1]Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014. Accessed September 10, 2014.

Resources and Information

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

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-Friday, from 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org
- Visit: www.LLS.org/informationspecialists.

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

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 certain eligible patients. For more information, please

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

Community Resources and Networking

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

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

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

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, locating summer camps and other needs. For more information, please visit www.LLS.org/resourcedirectory.

Clinical Trials (Research Studies). New treatments for patients with CML are under way. Many are part of clinical trials. 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
- Visit: www.LLS.org/clinicaltrials and click on TrialCheck®.

Advocacy. The LLS Office of Public Policy (OPP) enlists volunteers to advocate for policies and laws to speed 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 your doctor know if you need a language interpreter or 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/publications
  - Click on Childhood Blood Cancer and choose *Coping With Childhood Leukemia and Lymphoma*.
  - Visit: www.LLS.org/chapterfind 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: the VA (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 two-week period. For more information, please

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

Feedback. Like this booklet? Have suggestions? We'd love to know what you think. To tell us

- Visit: www.LLS.org/publicationfeedback
  - Click on "LLS Disease & Treatment Publications—Survey for Patients, Family and Friends."

Leukemia

Leukemia is a cancer of the marrow and blood. The four major types of leukemia are

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

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 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 Marrow* on page 39.

With acute lymphoblastic leukemia, the cancerous change begins in a marrow cell that normally forms lymphocytes (a type of white blood cell). With chronic myeloid leukemia, the cancerous change takes place in a marrow cell that normally forms red blood cells, some types of white blood cells and platelets.

The four main types of leukemia are further classified into subtypes. Knowing the subtype of your disease is important because your treatment plan is based, in part, on the subtype.

More general information about leukemia can be found in the free LLS publications *Understanding Leukemia* and *The CML Guide: Information for Patients and Caregivers.*

What is CML?

How CML Develops. Chronic myeloid leukemia (CML) is called by several other names, including

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

CML results from an acquired (not present at birth) or a genetic injury to the DNA of a single bone marrow cell. The mutated cell multiplies into many cells (CML cells). The result of the uncontrolled growth of CML cells in the marrow is an increase in the number of CML cells in the blood. CML does not completely interfere with the development of mature red cells, white cells and platelets. As a result, chronic phase myeloid leukemia is generally less severe than acute leukemia, and often patients do not have any symptoms when diagnosed.

Who is Affected by CML and Why?

Incidence. Most cases of CML occur in adults. From 2007 to 2011, the median age at diagnosis for CML was 64 years. A small number of children develop CML; the course of the disease is similar in children and adults. See *Children and Young Adults with CML* on page 33.

As shown in Figure 1 on page 7, the frequency of CML increases with age, from about less than 1.2 in 100,000 people until about 40 years, to about 2.4 in 100,000 people at 55 years, to about 9.6 in 100,000 people at 80 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 reached, or are approaching, the age range associated with increased CML incidence.

Chronic Myeloid Leukemia: Age-Specific Incidence Rates 2007-2011

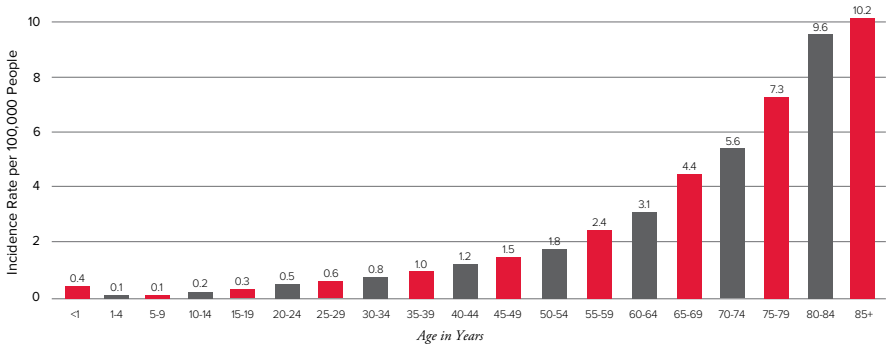


Figure 1. | The horizontal axis shows five-year age intervals. The vertical axis shows the frequency of new cases of CML per 100,000 people, by age-group. (Source: Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014. Accessed September 10, 2014.)

Causes. No one is born with CML. It happens when there is an injury to the DNA of a single bone marrow cell.

Risk Factors. Scientists do not yet understand why the *BCR-ABL* gene that leads to CML is formed in some people and not in others. However, in a small number of patients, CML is caused by exposure to very high doses of radiation. This effect has been most carefully studied in the survivors of the atomic-bomb blast in Japan. 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 go on to develop CML, and most people who have CML have not been exposed to high-dose radiation. Exposures to diagnostic dental or medical x-rays have not been associated with an increased risk of CML.

The Philadelphia Chromosome. A chromosome is an organized package of DNA found in the nucleus of the cell. Chromosomes are arranged in pairs. Chromosome pairs are made up of one chromosome from each parent. Humans have 23 pairs of chromosomes—22 pairs of numbered chromosomes, called "autosomes," and one pair of sex chromosomes (XX or XY).

CML was initially distinguished from other types of leukemia by the presence of a genetic abnormality of chromosome 22 found in the blood and marrow cells of patients with CML.

In 1960, doctors from the University of Pennsylvania School of Medicine in Philadelphia discovered the 22nd chromosome in people with CML was shorter than it was in healthy people. This shortened 22nd chromosome was later named the "Philadelphia chromosome" or "Ph chromosome."

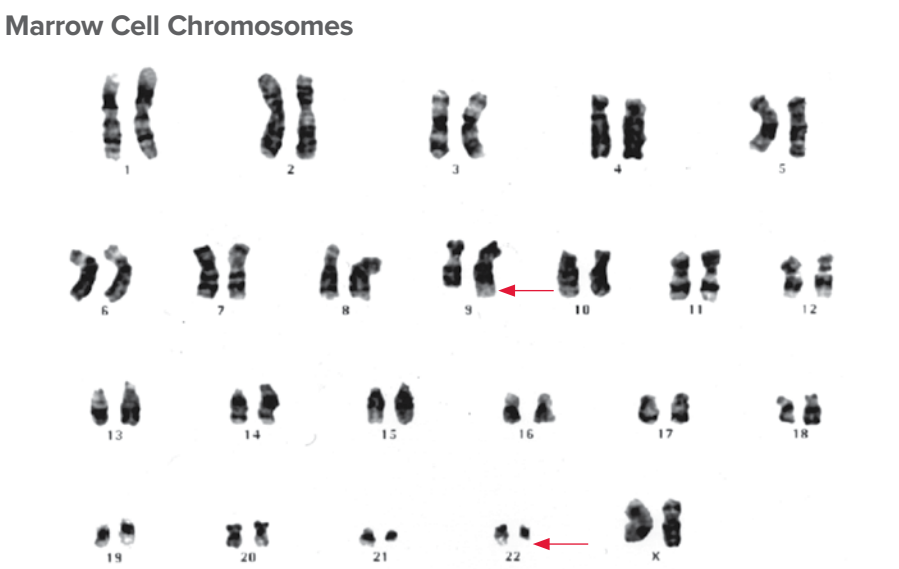


Figure 2. | Shown here is the set of chromosomes from a marrow cell of a female patient with CML. The higher the chromosome number, the smaller the chromosome. The arrow in the fourth row indicates the shortened arm of chromosome 22 (the Ph chromosome), characteristic of the leukemic marrow cells of 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.

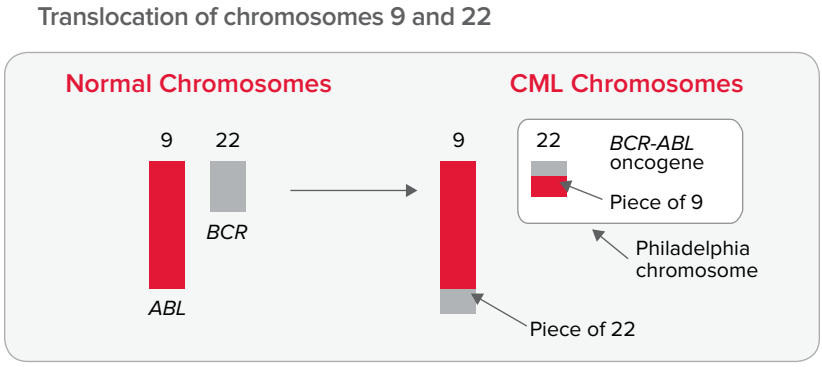
This figure kindly provided by Nancy Wang, PhD, University of Rochester Medical Center, Rochester, NY.

The *BCR-ABL* Cancer-Causing Gene (Oncogene). Further studies of CML cells established that two chromosomes, number 9 and number 22, were abnormal. Portions of these chromosomes actually switch places with each other. A portion of chromosome 9 moves to the end of chromosome 22; in addition, a portion of chromosome 22 moves to the end of chromosome 9. This exchange of parts of chromosomes is called "translocation" (see Figure 2). The translocation of chromosome 9 and chromosome 22 is found only in the leukemia cells of CML patients and in some patients with acute lymphoblastic leukemia (ALL). One theory that scientists propose about why this switch occurs is that when the cells are dividing, chromosomes 9 and 22 are very close to each other, making this error more likely.

The break on chromosome 9 leads to a mutation of a gene called *"ABL"* (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 fusion gene *BCR-ABL* (see Figure 3 on page 9). Genes provide cells with instructions for making proteins. The *BCR-ABL* gene produces a dysfunctional protein called

"BCR-ABL tyrosine kinase" (see Figure 4 on page 10). The BCR-ABL tyrosine kinase leads to the abnormal regulation of cell growth and survival and is responsible for the development of CML. For that reason, the BCR-ABL tyrosine kinase is a target for specific drug therapies that block its effects in many people with CML (see *Treatment* on page 15).

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 10).
- The abnormal enzyme protein is the principal factor in converting the marrow stem cell from a normal cell into a leukemic cell.

Figure 3. | The process of translocation between the genes on chromosome 9 and chromosome 22.

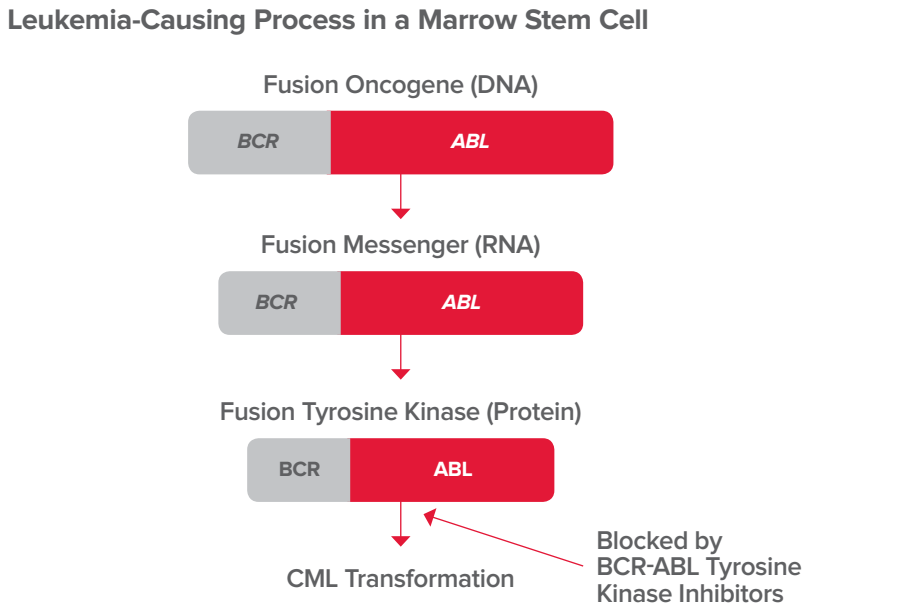


Figure 4. | The oncogene (cancer-causing gene) shown in the top bar is caused by the fusion of the *ABL* gene from chromosome 9 with the *BCR* gene from chromosome 22. The gene's DNA sequence is copied into messenger RNA, shown in the middle bar. The messenger RNA causes the formation of a mutant protein, an enzyme called "tyrosine kinase," shown in the lower bar. This enzyme triggers signals that cause the stem cell to act in an unregulated (leukemic) manner, leading to the formation of too many white blood cells that live too long. This results in the clinical manifestations of CML, such as high white blood cell counts and low red blood cell counts. Several BCR-ABL tyrosine kinase inhibitors, including imatinib mesylate (Gleevec®), dasatinib (Sprycel®) and nilotinib (Tasigna®), can bind to the BCR-ABL tyrosine kinase (protein) and block its effects. The specific drug action on the protein that leads to CML development is an example of "targeted therapy" (see *Treatment* on page 15).

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 symptoms. Those with symptoms often report

- Being very tired or tiring easily
- Shortness of breath during basic, everyday activities
- Unexplained weight loss
- Enlarged spleen or pain or dragging feeling on upper left side of abdomen under the ribs
- Being pale from anemia (a decrease in red blood cells)
- Night sweats
- Inability to tolerate warm temperatures.

Diagnosis

To diagnose CML, doctors use a variety of tests to analyze the blood and marrow cells.

Complete Blood Count (CBC). This test is used to measure the number and types of cells in the blood. People with CML often have

- Decreased hemoglobin concentration
- Increased white blood cell count, often to very high levels
- Possible increase or decrease in the number of platelets depending on the severity of the person's CML.

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

- Specific pattern of white blood cells
- Small proportion of immature cells (leukemic blast cells and promyelocytes)
- Larger proportion of maturing and fully matured white blood cells (myelocytes and neutrophils).

These blast cells, promyelocytes and myelocytes are normally not present in the blood of healthy individuals.

Bone Marrow Aspiration and Biopsy. These tests are used to examine 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 special needle is inserted through the hip bone and into the marrow to remove a liquid sample of cells. For a bone marrow biopsy, a special needle is used to remove a core sample of bone that contains marrow. Both samples are examined under a microscope to look for chromosomal and other cell changes. See *Health Terms* on page 42.

Cytogenetic Analysis. This test measures the number and structure of the chromosomes. Samples from the bone marrow are examined to confirm the blood test findings and to see if there are chromosomal changes or abnormalities, such as the Philadelphia (Ph) chromosome. The presence of the Ph chromosome (the shortened chromosome 22) in the marrow cells, along with a high white blood cell count and other characteristic blood and marrow test findings, confirms the diagnosis of CML. The bone marrow cells of about 90 percent of people with CML have a Ph chromosome 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 more sensitive method for detecting CML than the standard cytogenetic tests that identify the Ph chromosome. FISH is a quantitative test that can identify the presence of the *BCR-ABL* gene (see Figure 5). 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 chemicals each of which releases a different color of light. 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. Since this test can detect *BCR-ABL* in cells found in the blood, it can be used to determine if there is a significant decrease in the number of circulating CML cells as a result of treatment.

Identifying the *BCR-ABL* Gene Using FISH

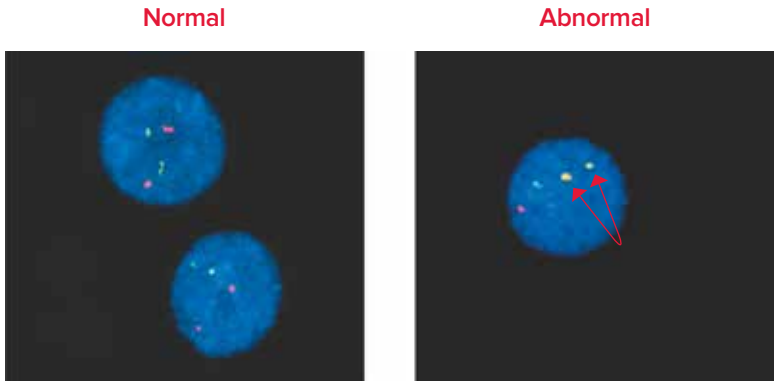


Figure 5. | Fluorescence in situ hybridization, or FISH, is a testing method that uses fluorescent molecules to mark the *BCR-ABL* gene in CML. In normal cells, two red and two green signals indicate the location of the normal *ABL* and *BCR* genes, respectively. In abnormal cells, the *BCR-ABL* fusion is visualized through the fusion of the red and green signals. It is frequently detected as a yellow fluorescence (noted by arrows).

Polymerase Chain Reaction (PCR). The *BCR-ABL* gene is also detectable by molecular analysis. A quantitative PCR test is the most sensitive molecular testing method available. This test can be performed with either blood or bone marrow cells. The PCR test essentially increases or "amplifies" small amounts of specific pieces of either RNA or DNA to make them easier to detect and measure. So, the *BCR-ABL* gene abnormality can be detected by PCR even when present in a very low number of cells. About one abnormal cell in one million cells can be detected by PCR testing.

Quantitative PCR is used to determine the relative number of cells with the abnormal *BCR-ABL* gene in the blood. This has become the most used and relevant type of PCR test because it can measure small amounts of disease, and the test is performed on blood samples, so there is no need for a bone marrow biopsy procedure.

Blood cell counts, bone marrow examinations, FISH and PCR may also be used to track a person's response to therapy once treatment has begun. Throughout treatment, the number of red blood cells, white blood cells, platelets and CML cells is also measured on a regular basis (see *Measuring Treatment Response* on page 26).

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

Phases of CML

Doctors use diagnostic testing to determine a patient's phase of CML. There are three phases of CML. They are

- Chronic phase
- Accelerated phase
- Blast crisis phase.

A small number of patients progress from chronic phase, which can usually be well managed, to accelerated phase or blast crisis phase. This is because there are additional genetic changes in the leukemic stem cells. Some of these additional chromosome abnormalities are identifiable by cytogenetic analysis. However, there appear to be other genetic changes (low levels of drug-resistant mutations that may be present at diagnosis) in the CML stem cells that cannot be identified by the laboratory tests that are currently available.

Chronic Phase. In the chronic phase, fewer than 10 percent of the cells in the blood and bone marrow are immature white blood cells (blasts).

People with chronic phase CML

- May or may not have symptoms.
- Have an increased number of white blood cells.

When treated, the

- Symptoms resolve quickly.
- White blood cell counts return to near-normal levels.

- Spleen reduces in size.
- Hemoglobin concentration improves.
- General well-being of a patient is restored and normal activities can continue.

Accelerated Phase. In this phase, the number of blast cells in the peripheral blood and/or bone marrow is higher than normal.

People with accelerated phase CML

- Have an increased white blood cell count due to the accumulation of blast cells
- Have a decrease in the number of platelets
- May have new chromosome changes (mutations)
- May develop new or have worsened anemia
- Experience fatigue
- Have an enlarged spleen
- Develop a loss of well-being and may not feel well
- Have other complications.

Blast Crisis Phase. In this phase, the number of blast cells increases in both bone marrow and blood.

People with blast crisis phase CML

- Have low red blood cell, platelet and neutrophil counts
- See the spread of blast cells outside the blood and/or the bone marrow and into other tissues
- Experience symptoms such as
  - Fatigue
  - Shortness of breath
  - Abdominal pain
  - Bone pain
  - Spleen enlargement
  - Bleeding
  - Infections.

In about 25 percent of people with CML, the blast crisis phase resembles

acute lymphoblastic leukemia; however, in most people, it looks like acute myeloid leukemia.

Risk Assessment. The CML phase and other factors are used in determining treatment and can also help predict CML outcome. These are known as "prognostic factors."

Two prognostic scoring systems are 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.
- 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 blood.

Based on their risk assessment scores, patients are classified into low-, intermediate- or high-risk groups. Doctors use risk scores to help guide treatment decisions. These scores have also been used to classify patients into risk groups in some of the clinical trials that evaluate CML drug therapies. For more information on the Hasford and Sokal scoring systems, see pages 46 and 50 in the *Health Terms* section.

Treatment

Doctors who specialize in treating patients with CML are called "hematologist/oncologists." 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 at least two decades. See Table 1 on page 19.

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 approach for treating each patient is customized, based on the phase of CML at diagnosis, test results, risk scores and age, particularly if stem cell transplantation is a consideration.

High White Blood Cell Counts. Some patients may have very high white blood cell counts at the time of diagnosis. This can create viscosity (thickness and stickiness of blood) problems and impair blood flow to the brain, lungs, eyes and other sites and also cause damage in small blood vessels.

Patients can be treated, at first, in two ways.

- Hydroxyurea (Hydrea®) is an oral medication that is often used to decrease the white blood cell count.
- Leukapheresis, the removal of white blood cells by a machine that is similar to a dialysis machine. Leukapheresis can be used 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 34.

Treatment for Chronic Phase CML. (*For treatment information about accelerated phase and blast crisis phase CML*, see page 23.) The initial goal in treating people with chronic phase CML is to restore blood counts to normal levels. This is followed by a more profound reduction or elimination of CML cells altogether, while keeping an acceptable quality of life.

Treatment

- Usually returns the blood cell counts to normal values within one month and maintains them either at or close to normal levels (slightly lower levels in blood cell counts are not uncommon)
- Reduces the size of the spleen quickly until it approaches its normal size
- Helps prevent infections and abnormal bleeding
- Allows patients to resume their previous levels of day-to-day activities.

Patients will need to receive periodic health checks, including blood cell counts and other tests to determine the extent and stability of cytogenetic and molecular remission (see *Measuring Treatment Response* on page 26). Periodic bone marrow examinations may be necessary early in treatment but can often be done less frequently over time; periodic blood-based monitoring of treatment response by PCR continues indefinitely. Individuals also need to have their tolerance to drugs assessed from time to time and may need dosage adjustments.

Tyrosine Kinase Inhibitor Therapy. Tyrosine kinase inhibitors (TKIs) are drugs that target the abnormal BCR-ABL protein that causes the uncontrolled CML cell growth. This protein, made by the *BCR-ABL* gene, is located on or near the surface of cells and is called a "tyrosine kinase." TKIs inhibit (block) the BCR-ABL protein from sending the signals that cause the growth of abnormal cells. Three TKI drugs are approved as initial therapy (first-line treatment) for chronic phase CML and all three are good options for newly diagnosed patients. 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 either intolerance or resistance to the 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) is offered to the patient.

Other TKI options for treatment include

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

Imatinib mesylate (Gleevec®).

- This highly effective oral drug therapy brings about a stable remission in most people.
- It is the oldest TKI therapy drug.
- Gleevec has been the standard initial therapy (first-line treatment) for chronic phase CML since 2001 (see Table 1 on page 19).
- Studies have shown that Gleevec keeps the chronic phase of CML under control for at least 10 years, which is the longest publicized observation period since its approval (in 2001).
- Gleevec® has been approved by the US Food and Drug Administration (FDA) to treat
  - Newly diagnosed adult patients with Ph+ CML in chronic phase
  - Adults with Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Interferon is only used as an initial therapy in special circumstances (e.g., CML that is newly diagnosed during pregnancy).
  - Newly diagnosed pediatric patients with Ph+ CML in chronic phase.

The drug is generally well tolerated by the majority of both younger and older patients, although most people experience some side effects. For some people with CML, the side effects of Gleevec are significant and limit their ability to take the drug or prevent them from taking the drug. In addition, some CML patients develop disease that no longer responds to Gleevec, and therefore requires other therapies.

Fortunately, there are other approved therapies that help people with CML who are Gleevec-intolerant or Gleevec-resistant. When Gleevec is not a treatment option, doctors decide, along with their patients, which of the other treatments will be the best alternative. That decision will be based on specific knowledge about the person's pattern of resistance and the potential side effects of each drug.

Dastinib (Sprycel®) and nilotinib (Tasigna®).

- Sprycel and Tasigna were both approved in 2010 for newly diagnosed chronic phase CML patients.
- To date, neither Sprycel nor Tasigna has been shown to result in longer survival.
- Findings from studies of each drug show faster complete cytogenetic response (CCyR) and molecular response (MR) than the response from Gleevec. These drugs may prove to be associated with better long-term outcomes.
- Both drugs are approved to treat chronic and accelerated phases of CML in adults who are either resistant to, or intolerant of, prior therapy that included Gleevec.
- Sprycel is also approved to treat blast crisis phase CML in adults with either resistance or intolerance to prior therapy that included Gleevec.

People being treated with Sprycel or Tasigna should note that it is important to follow the specific instructions for taking these drugs, as these may differ from instructions for Gleevec, which is typically taken with a meal once daily. Sprycel is taken once daily, but it can be taken either with or without food. Tasigna is taken twice daily, but on an empty stomach.

Bosutinib (Bosulif®) and ponatinib (Iclusig®).

- Bosulif was approved in 2012 to treat adults in all phases of CML with resistance or intolerance to prior therapy, including Gleevec.
- Iclusig was approved in 2012 for the treatment of adults with T315I mutation and adults for whom no other TKI is indicated.
- Both drugs bind to the BCR-ABL tyrosine kinase more effectively than other TKIs, making them useful for many patients whose disease is resistant to Gleevec therapy.

TKI Resistance. Identifying the type of mutation responsible for resistance can help a doctor decide which drug to prescribe. More than 50 percent of Gleevec resistance is thought to result from the presence of subtle mutations in the BCR-ABL protein, which affects Gleevec's ability to bind to the protein and shut off its activity. When this happens, Sprycel, Tasigna, Bosulif and Iclusig can be alternative treatments.

CML patients with certain mutations may not respond to Sprycel or Bosulif, while patients with other mutations may not respond to Tasigna. For instance, patients with Gleevec-resistant mutations V299 and F317 are not likely to respond to Sprycel or Bosulif and should be treated with Tasigna or Iclusig instead. Similarly, patients with Gleevec-resistant mutations G250, Y253, E255 and F359 are not likely to respond to Tasigna and should be treated with Sprycel, Bosulif or Iclusig.

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 with T315I mutation and adults for whom no other TKI is indicated
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®)

Table 1. | Some of the drugs used to treat CML.

Side Effects of TKI Therapy. TKI treatment often has side effects. Like any drug, the side effects depend on the patient's age and health, the type of drug and dosage. Fortunately, most side effects can be managed or even prevented and the benefit of CML remission generally outweighs the risk of side effects. If patients are experiencing any side effects, they should let members of their healthcare team know right away because they will be able to provide necessary help. Managing side effects is important for the patient's quality of life and the CML treatment outcome.

Side Effects of Gleevec. Gleevec therapy may bring about a variety of side effects. For most people, these side effects can be managed without stopping therapy. Common side effects from Gleevec may include

- Fluid retention (edema)
- Puffiness around the eyes
- Nausea and vomiting
- Muscle cramps
- Diarrhea
- Rash
- Chronic fatigue
- Possible cardiac effects (see page 22 for more information).

Gleevec primarily inhibits three of the 90 human tyrosine kinases. In most patients, the principal effect of the drug is on the mutant BCR-ABL tyrosine kinase in CML cells. However, it is possible that normal cells are also affected, which may cause these and other side effects.

A "late effect" of treatment is a medical problem that does not show up or get noticed until years after the initial treatment. A rare but potential late effect of Gleevec therapy is the loss of the mineral phosphorus from bone which may lead to osteoporosis. Osteoporosis is a condition in which the normal balance of bone buildup and breakdown (an ongoing process in the body) shifts slightly—there is more bone breakdown and less bone buildup. Patients need to be monitored for this condition and any other side effects.

Side Effects of Sprycel. In a one-to-one comparison with Gleevec, most side effects were reported less commonly in patients treated with Sprycel. Common side effects from Sprycel may include

- Low white blood cell and platelet counts
- A collection of fluid around the lungs (pleural effusion)

- Diarrhea
- Headache
- Fluid accumulation (edema)
- Low blood calcium levels
- Slight abnormalities in liver function test results
- An increased, yet rare risk of a serious condition called "pulmonary arterial hypertension" (PAH), high blood pressure in the arteries of the lungs
- Possible cardiac effects (see page 22 for more information).

Side Effects of Tasigna. In a one-to-one comparison with Gleevec, most side effects were reported less commonly in patients treated with Tasigna. Common side effects from Tasigna may include

- Low white blood cell and platelet counts
- Pancreatic enzyme abnormalities
- Occasional pancreatitis
- Low blood phosphorus levels
- Abnormalities in liver enzymes, including increased bilirubin levels
- Hyperglycemia
- Rash
- Nausea
- Headache
- Itching
- Tiredness
- Diarrhea
- Constipation
- An increased risk of vascular events (disease relating to blood vessels), such as a relatively rare but serious condition called "peripheral arterial occlusive disease" (PAOD), a narrowing of blood vessels that restricts blood flow
- Possible cardiac effects (see page 22 for more information).

It is important for researchers to continue to evaluate the long-term safety of all approved TKIs. For more information about the side effects of Gleevec, Sprycel or Tasigna, speak to your doctor and see the full prescribing information for these medications.

Side effects of Bosulif and Iclusig. Common side effects of Bosulif and Iclusig can be easily prevented or managed with appropriate supportive medication. However, Iclusig is only prescribed for patients for whom no other TKI therapy is indicated. They may include

- Diarrhea
- Nausea
- Vomiting
- Severe liver toxicity
- Serious vascular events, such as arterial thrombosis.

Cardiac Effects. Patients with a history of cardiac disease need to be monitored carefully and frequently. It is unusual, but some patients who were treated with Gleevec, Sprycel and/or Tasigna have developed serious side effects such as

- Severe congestive heart failure (a weakness of the heart that leads to a buildup of fluid in the lungs and surrounding body tissues)
- Left ventricular dysfunction (difficulty emptying blood from the left lower chamber of the heart).

A recent trial studying the potential long-term effects among a large group of CML patients who were on Gleevec therapy indicated that many of the patients who developed adverse cardiac effects also had other health problems and risk factors, including older age and a medical history of cardiac disease or they had received prior treatment with cardiotoxic drugs.

A possible side effect of Tasigna, a drug that needs to be regularly monitored, is a potential heart rhythm called "QT prolongation." This condition causes an irregular heartbeat and may be life threatening. Gleevec and Sprycel may occasionally cause QT prolongation in a small number of individuals. Some other medications are also known to cause QT prolongation, and should be avoided whenever possible. Your doctor will give you a list of medications to avoid, and will monitor you for these conditions, as needed, before and during treatment. An electrocardiogram (ECG) is recommended for patients taking QT interval-prolonging medication.

Protein Synthesis Inhibitor Therapy. Omacetaxine (Synribo®) a non-TKI, chemotherapy drug, is approved for chronic and accelerated phase CML patients with resistance or intolerance to at least two prior TKIs.

Synribo is administered through injection under the skin. The most common side effects include

- Low red and white blood cell counts

- Low platelet counts
- Diarrhea
- Nausea
- Fatigue
- Fever
- Infection
- Reaction at the injection site.

Other CML Drug Therapies. These drugs were used as initial therapy before TKIs were available. They may be continued in select patients and are still options in patients who are either intolerant of, or resistant to, all of the FDA-approved treatments.

The oral medication hydroxyurea (Hydrea®) is used in some patients to lower their white blood cell count before starting a TKI.

Interferon is an injectable immunotherapy medication. This medication often cannot be tolerated and may have more side effects than TKIs, especially when given to older patients. Side effects can include

- Flulike symptoms such as fever, muscle aches and weakness
- Prolonged fatigue and weight loss, which may require a reduction in dosage
- Hair loss
- Diarrhea
- Depression
- Ulceration of the lining of the mouth
- Cardiac effects
- Other side effects that occasionally occur.

Interferon administered in combination with TKIs is under study. This approach may offer some benefit; a small proportion of patients who had deep remissions on interferon 20 years ago remain free of CML even though they stopped taking interferon after a few years. However, because of its side effects, interferon is not a good option for most CML patients.

Treatment for Accelerated Phase and Blast Crisis Phase. The goal in treating accelerated or blast crisis phase CML is, as with the chronic phase, to eliminate all cells that contain the *BCR-ABL* gene, leading to remission. If this is not possible, the goal is to return the disease to the chronic phase.

Treatment options for patients with accelerated phase or blast crisis phase CML include

- Gleevec, commonly used as an initial treatment
- Sprycel and Tasigna, for Gleevec-resistant patients who progress to accelerated or blast crisis phase during the course of Gleevec treatment
- Sprycel, Tasigna and Bosulif—also believed to represent reasonable options for patients
- Synribo, approved for patients in accelerated phase who either no longer respond to or cannot tolerate two or more TKIs. This may be an alternate choice for patients.

Prior to these therapy options, allogeneic stem cell transplantation was the principal means of successful treatment for patients of an appropriate age, in generally good health and with an available donor.

Stem cell transplantation is still a treatment option for some patients who are first diagnosed in, or progress to, advanced phases of CML (see *Stem Cell Transplantation* below). These patients are counseled by their doctors to weigh the benefits and risks of having an allogeneic stem cell transplant while they are still in remission after their initial Gleevec treatment and particularly after second-line treatment with Sprycel. Although not approved for the treatment of patients with newly diagnosed blast phase CML, Sprycel, Tasigna and Bosulif can be effective and patients can achieve initial remissions that can facilitate transplantation. The outlook for patients with blast phase CML who do not undergo transplantation while in remission is quite poor.

Stem Cell Transplantation. There are two types of stem cell transplantation, allogeneic stem cell transplantation, which is curative for some CML patients and autologous stem cell transplant, which is rarely used in CML.

Allogeneic Stem Cell Transplantation. Allogeneic stem cell transplantation (infusion of donor stem cells into a patient) is the best-documented curative treatment for CML at this time. The decision to pursue allogeneic transplantation has become more complicated because many patients have a very good response 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 to a greater extent than transplantation.

The transplant patient receives drug therapy first to induce a remission or, in advanced phase cases, to return to chronic phase CML. This is followed by high-dose conditioning chemotherapy and then the transplant. This approach increases the likelihood of successful remission after transplantation, assuming that drug side effects are minimal.

Several factors are considered in determining whether or not a CML patient is a good candidate for transplantation. These include the

- Patient's age
- Patient's general health
- Current CML phase
- The response to prior TKI therapy
- The availability of a well-matched donor.

Allogeneic transplantation is recommended for patients who have the T315I mutation that do not respond to therapy with TKIs.

Although transplants are typically more successful in younger patients, there is no specific age cutoff for stem cell transplantation. There are certain risk factors for transplants. These include

- Mortality—20 percent of patients who undergo stem cell transplantation will die from complications of the procedure within one to two years.
- Of those who are cured, many experience chronic toxicities, which can be debilitating in some cases.

About 70 percent or more of those who undergo allogeneic stem cell transplantation are cured of their CML.

Donor Lymphocyte Infusion (DLI). A DLI is a procedure in which a patient who has relapsed after the transplant may be given an infusion of lymphocytes from the original stem cell donor. This may induce a more intense immune reaction against the recipient's CML cells. DLI has been found to be more effective in patients who have chronic phase relapse than in those who have advanced phase relapse.

"Graft-versus-host disease" is a potential side effect of this therapy. This happens when the infused (donor) immune cells perceive the cells in the patient's body as foreign and then attack them. It causes potentially serious side effects. Still, most patients have good results from DLI.

Autologous Stem Cell Transplantation. Autologous stem cell transplantation (in which a person's own marrow or blood is the source of the stem cells) is rarely, if ever, used to treat people with CML, given the limited benefit of this method as concluded from long-standing studies.

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

Research and Clinical Trials. For information on other treatment options that are either being researched or are in clinical trials, please see page 36.

Measuring Treatment Response

Measuring the response to treatment with blood and bone marrow testing is a very important part of treatment for people with CML. In general terms, the greater the response to drug therapy, the longer the disease will be controlled. Other factors that affect a person's response to treatment include

- The stage of the disease
- The features of the individual's CML at the time of diagnosis.

Nearly all people with chronic phase CML have a "complete hematologic response" with Gleevec, Sprycel or Tasigna therapy; most of these people will eventually achieve a "complete cytogenetic response." Patients who have a complete cytogenetic response often continue to have a deeper response and achieve a "major molecular response." Additionally, a growing number of patients achieve a "complete molecular response." (For an explanation of these terms, see Table 2 on page 28.)

People who are taking Gleevec can feel confident and be encouraged to continue therapy based on the safety data from more than 10 years of clinical trials. Longer-term safety data have also been reported for Sprycel (approved in 2006) and Tasigna (approved in 2007) in patients with Gleevec resistance or intolerance. In addition, the findings from the ongoing, careful monitoring for long-term or late effects is reassuring so far.

Adherence to Therapy. Treatment for CML has changed since 2001 with the introduction of oral TKI therapies. It is important for patients to continue taking their medication to get the best response. Unless they are following their doctor's instructions, stopping medication or taking less than the amount prescribed can impact how well the medication works and may result in a loss of response and an unfavorable treatment outcome.

For patients with CML, adhering to treatment is associated with the probability of achieving and improving long-term outcomes, including achieving a major molecular response and improved survival. Good adherence means that a patient follows all of the doctor's recommendations, including

- Taking the appropriate number of pills as ordered: at the right time, on the right day, every day
- Reporting any side effects so that supportive treatment can be administered.

In order to achieve the best possible results, the patient and members of the treatment team must work together in choosing a treatment that fits into the patient's normal routine in the best possible ways. CML patients should also let their treatment team members know if there are any problems (including side effects) that make it difficult for them to take the medication as prescribed. Generally, these difficulties can be either managed or completely overcome.

Blood and Marrow Tests. During CML drug therapy, a complete blood count (CBC) is routinely performed to measure the numbers of white blood cells, red blood cells and platelets. Hemoglobin and hematocrit levels are also measured. After an initial diagnosis of CML, blood counts may be performed every two to four weeks. Once blood counts return to normal levels, blood tests will generally be performed every three to six months.

Blood or bone marrow may be used for fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) tests (see pages 44 and 49). In general, FISH is not commonly used to track disease response in most patients. Quantitative PCR testing is generally performed at diagnosis and every three months after initiation of therapy.

Certain changes can occur in CML cells in the bone marrow that cannot be detected by blood tests. Bone marrow tests are generally recommended

- After three months in patients who do not have access to a *BCR-ABL* PCR test
- At 12 months in patients who have not yet achieved either a complete cytogenetic or a major molecular response.

After achievement of a complete cytogenetic response, bone marrow testing can be performed infrequently. Anytime there is a substantial change in response to oral CML drug therapy as measured in the blood, a bone marrow test is recommended to determine if there are specific cell and chromosome changes that cannot be detected by blood tests (see Table 3 on page 29). Note that the same individual may have a deep remission with stable, low levels of *BCR-ABL* (e.g., complete molecular response) according to one lab's test results and yet still have detectable *BCR-ABL* levels according to another lab's test results. Efforts to standardize quantitative PCR reporting using an International Scale standard are ongoing in an effort to more uniformly report test results.

The International Scale (IS) defines the standard baseline as *BCR-ABL* 100% (IS). This level was arrived at by averaging the number of *BCR-ABL* gene molecules from 30 newly diagnosed chronic phase CML patients. Reductions in the level of *BCR-ABL* genes are reported as "log reductions" and expressed as a percentage.

- A 1-log reduction indicates that the *BCR-ABL* levels have decreased to 10 times below the standardized baseline. This is also written as *BCR-ABL* 10%. This reduction is approximately equivalent to a major cytogenetic response.
- A 2-log reduction means that *BCR-ABL* levels have decreased to 100 times below the standardized baseline or *BCR-ABL* equals 1%. This reduction is approximately equivalent to a complete cytogenetic response (CCyR).
- A 3-log reduction indicates that the *BCR-ABL* levels have decreased to 1,000 times below the standardized baseline or *BCR-ABL* equals 0.1%, which is also known as a "major molecular response" (MMR).

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
	Partial cytogenetic response (PCyR)	1%-35% of cells have Ph chromosome	
	Major cytogenetic response	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 at the start of treatment.

Table 2. | This table describes the range of responses to CML treatment.
Source: The NCCN Clinical Practice Guidelines in Oncology™ for Chronic Myelogenous Leukemia.

For people who experience a loss of response to a TKI, or those who do not achieve the expected response within a given period of time (see Table 3 on page 29), 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	Complete hematologic response (CHR) Partial cytogenetic response (PCyR)	• Continue treatment at same dosage • Monitor with quantitative PCR (QPCR) every 3 months	• Evaluate patient compliance • Perform 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)
6 months	Continued complete hematologic response (CHR) Partial cytogenetic response (PCyR) or better	• Continue treatment at same dosage • Monitor with QPCR every 3 months	• Evaluate patient compliance • Perform gene mutation testing **THEN** Increase TKI dosage (if possible) **OR** Change to alternate TKI **OR** Enter clinical trial **OR** Evaluate for HSCT

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 3 years and every 3-6 months thereafter	• Evaluate patient compliance • Perform 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 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 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

Table 3. | 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: CML Guidelines Updated. *The NCCN Clinical Practice Guidelines in Oncology™ for Chronic Myelogenous Leukemia.*

Patients respond differently to CML drug therapy. These are general guidelines for CML drug therapy. An individual's CML drug therapy response is measured against that person's 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 later than "after three months of 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.

BCR-ABL Gene Mutation Testing

Patients should talk to their doctor about ordering a gene mutation test if there is

- Failure to meet a treatment milestone
- Loss of hematologic or cytogenetic response despite taking an adequate dosage of a TKI
- Unexplained confirmed rise in quantitative PCR level by a factor of 5 to 10
- Concerns about the medication not being effective (not working).

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

Patients should consider checking in with a CML specialist from time to time to make sure they are meeting their treatment milestones. Patients can arrange for a consultation on their own or can ask their doctor to work in consult with a CML specialist. Patients who belong to a health maintenance organization (HMO) typically have more restrictions on their ability to seek consultation with academic medical centers. Speak to your insurance company to know what options are covered under your plan.

The patient's doctor can send the patient's blood sample for *BCR-ABL* PCR testing (which requires specialized equipment and expertise) to

- A reference laboratory (used for specialized tests that are ordered only occasionally or require specialized equipment)
- An academic center
- An NCI (National Cancer Institute) center laboratory.

There are commercial tests available for detecting BCR-ABL kinase domain mutations. Many health insurance plans require that patients use a specific lab, which is often indicated on the patient's insurance card. Sometimes, if the insurance company will not cover the test, providing clarification or justification for the testing may help the patient's case. The National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN) have suggestions for when to assess for mutations. Some insurance carriers consider mutation assessment a "genetic" test and will only authorize a single such test per lifetime. Patients should talk to their doctors and members of their healthcare teams to ensure that, if needed, the mutation testing will be covered by their insurance companies.

For information about the CML mutation testing guidelines from the NCCN, please visit www.nccn.org/patients/guidelines/cml/index.html#2.

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.

While CML appears to have the same disease course in children as it does in adults, there are no specific guidelines for CML treatment in children yet. The features of disease at diagnosis and the response to therapy in children seem to be similar to that in adults.

Imatinib mesylate (Gleevec®) is the primary treatment used for children diagnosed with CML. More than 80 percent of children with chronic phase disease treated with Gleevec achieve complete cytogenetic response.

Although there are not a great number of studies focused on the treatment of pediatric patients with CML, there is evidence that TKI drugs, such as Gleevec, may slow growth, particularly for children treated before they reach puberty. Stopping treatment with Gleevec can result in catch-up skeletal growth (when the body begins to grow again after a period of slowed development). Careful monitoring of the child's height and overall growth during and after treatment is recommended.

Other treatment options for children who have CML and do not respond well to Gleevec may be treatment with other tyrosine kinase inhibitors (TKIs), and, possibly stem cell transplantation. Currently, other TKIs such as dasatinib (Sprycel®) or nilotinib (Tasigna®), are used. When resistance to a TKI is observed, then analysis for specific resistance-causing mutations is commonly performed. Complications of a transplant remain challenging, so treatment with Gleevec continues to be the first choice for younger patients in chronic phase despite the potential side effects associated with its use.

With oral medications, it is important to follow the doctor's directions and keep taking the medication for as long as prescribed. This can be overwhelming for parents of children and young adults because remembering to take the drug consistently and as ordered can be hard at times.

Talk to your child's doctor about the best treatment for him or her 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 publications *Choosing a Blood Cancer Specialist or Treatment Center* and *Coping With Childhood Leukemia and Lymphoma* for more information.

Fertility, Pregnancy and TKIs

The overall data regarding CML treatment during pregnancy is limited. According to the limited data available, the best outcomes for pregnancy in CML patients occur when patients and their doctors plan for a pregnancy and develop a treatment strategy where mother and baby are carefully monitored and protected. Given the generally favorable longer-term outcome with TKI therapy, a growing number of men and women with CML who are of reproductive age and are in stable remission with ongoing treatment are increasingly interested in conceiving.

Data are available from a limited number of pregnancies that have occurred accidentally in women who were taking Gleevec. While many children who were exposed to Gleevec in the uterus have been born healthy and without apparent abnormalities, there have been a few abnormalities noted both in live births and in aborted or miscarried fetuses. Regarding specific use of drugs, there is no data to suggest that Gleevec or any other TKI drug can be taken safely during pregnancy. Current recommendations include counseling so that potential parents understand the

- Need for women to stop treatment during preconception and pregnancy
- Risk of relapse, if therapy is stopped, based on the depth and duration of response
- Risk for fetal effects from Gleevec and other TKI drugs (probably greatest during the first trimester)
- Need for women on TKI therapy to refrain from breast-feeding their babies
- Uncertainty about treatment options and restoration of stable response during and after pregnancy.

Early reports of treatment cessation (stopping treatment) for pregnancy have been discouraging; risk of relapse and the chance of regaining response remain unknown. With a larger proportion of patients in stable remission and promising results from early trials of deliberate treatment cessation among a nonpregnant population, hope remains that women with CML who want to become pregnant can be better managed with lower risk to both mother and child if treatment is interrupted after achieving a deep and stable molecular response. See *Treatment Cessation* on page 35. Experience has been even more limited for other TKI drugs such as Sprycel and Tasigna. Like Gleevec, these agents are considered unsafe to take during pregnancy. Women who are taking Sprycel or Tasigna should not breast-feed. There is hope that by achieving deep molecular responses in a higher proportion of patients that these new agents may facilitate more treatment interruptions, but this issue is not yet resolved.

Data are limited on men who father children while taking Gleevec or other TKIs. To date, there are no obvious causes for concern for men taking TKIs that warrant

a formal contraindication for fathering a child. Nonetheless, these drugs cannot be presumed safe in this setting and, before deciding to start a family, men in treatment for CML are encouraged to discuss the matter with their doctor. In addition, TKI drugs have the potential to affect a man's ability to conceive a child, especially after long-term use. Men of reproductive age should discuss their fertility concerns and available options with their doctor, including the cryopreservation of sperm (sperm banking) before the start of TKI therapy.

Treatment Cessation

Although many patients with chronic phase CML develop deep and lasting remission with drugs such as Gleevec, Sprycel and Tasigna, CML is not generally believed to be cured with current medical therapies. PCR testing shows that most patients with deep remissions still have evidence of residual CML cells. Even if patients test negative for the *BCR-ABL* gene by PCR testing, it should be noted that PCR cannot sample every last cell in the blood and bone marrow. Even when PCR does not detect any evidence of *BCR-ABL* after the initial treatment, CML drug therapy is continued to treat the disease that presumably remains.

Limited reports in past medical literature about treatment cessation (stopping treatment) demonstrated that relapse is common or even to be expected. Clinical trials have begun to examine whether individuals who have deep remissions while taking therapy are able to sustain stable remissions after they stop therapy (see *Measuring Treatment Response* on page 26). Interestingly, approximately 40 percent of patients with undetectable disease who have interrupted treatment have not shown any evidence of disease recurrence during the following five years, but it is not known if any of these patients are truly cured of their CML. More research is required in this area before any change can be confidently made to the current recommendation to maintain therapy indefinitely. Hence, the ability to detect minimal residual disease with high sensitivity is crucial when determining eligibility for treatment cessation trials and to identify the loss of molecular response.

There have been rare individuals who were treated with Gleevec alone and remained free of detectable disease for several years despite discontinuing this medication and in the absence of any CML therapy. However, it is possible that interruption of TKI therapy, even in patients with undetectable disease, may increase the likelihood of developing resistant disease; therefore, prolonged TKI interruption should only be performed under special circumstances such as a clinical trial. For Gleevec-responsive individuals, the risk of losing response—or moving to a more advanced phase of the disease—appears greatest during the first four years after beginning treatment. After this early period, the risk appears to decrease to very low levels. Available evidence suggests that people who respond to TKIs may remain in remission for very long periods. However, patients who are interested in stopping treatment should only do so within the confines of a clinical trial.

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.

Clinical trials are designed to be accurate and very safe. There are clinical trials for newly diagnosed patients and for patients who have already been treated. 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. Information Specialists can search for clinical trials on behalf of patients, family members and healthcare professionals. This search service is also available at www.LLS.org/clinicaltrials.

Research Approaches. There are clinical trials for newly diagnosed patients, patients with advanced phase disease or patients who are either intolerant of, or resistant to, their current treatment. In light of the success of TKI therapy in treating most chronic phase CML patients, ongoing research studies are largely aimed at assessing whether patients with a stable complete molecular response can safely discontinue treatment, or if it is possible to add agents that help eradicate the few residual CML cells that presumably persist in all patients in remission.

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

Drug Therapy. Bafetinib is a dual BCR-ABL and LYN kinase inhibitor, developed as a third-line treatment for patients with CML and certain forms of acute lymphoblastic leukemia. It is currently being studied in clinical trials where it is showing promising results in patients with Ph+ CML and other Ph+ leukemias that are either intolerant of, or resistant to, Gleevec and second-line therapies.

TKI Discontinuation Studies. Several studies are evaluating the ability of patients with a stable complete molecular response to interrupt TKI therapy and experience a treatment-free remission. These studies may eventually lead to improved confidence in the potential long-term safety of this approach, but at the present time, treatment discontinuation should not be pursued outside the context of a clinical trial.

Disease Eradication Strategies. Many lab studies have found potential treatments that may help eradicate the few remaining CML cells in most patients treated with TKIs, and hopefully cure patients so that they may discontinue medical therapies altogether. One area involves inhibitors of a protein called "smoothened" (SMO) in combination with BCR-ABL TKIs. A number of additional pathways are being studied, and efforts to assess their importance in CML patients are ongoing.

Given that chronic phase CML is generally a slowly progressive disease, even in the absence of effective therapy, it will likely be many years before it is known whether strategies aimed at disease eradication truly achieve disease cure.

Vaccine Therapy. Various forms of vaccine therapy are being studied. Proteins on the surface of CML cells may be well-suited targets for such vaccines, which could employ a patient's immune cells to attack his or her own CML cells. See the free LLS publication *Immunotherapy Facts* for information about the development of blood cancer vaccines.

Reduced-intensity Stem Cell Transplantation. A modified form of allogeneic transplantation called "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 dosages of chemotherapy drugs and/or radiation in preparation for the transplant, compared to the dosages 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-tumor effect would still occur.

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

In addition, research is under way 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 publication *Blood and Marrow Stem Cell Transplantation.*

CML-Related Disorders

There are other subtypes of myeloid leukemia that have a chronic course (progress more slowly) and have some of the signs and symptoms of CML. These include

- Chronic myelomonocytic leukemia (CMML)
- Juvenile myelomonocytic leukemia (JMML)
- Chronic neutrophilic leukemia (CNL).

These diseases are less common "myeloproliferative neoplasms." People with these diseases do not have the *BCR-ABL* gene; the absence of the *BCR-ABL* gene is one of several distinguishing features used to make the correct diagnosis.

In general, CMML, JMML and CNL create more severe changes in blood cell counts early in the course of the disease; these changes are not as well controlled with current drug treatments.

People with some signs and symptoms of CML who are *BCR-ABL* negative and do not fit the diagnostic criteria for CMML are sometimes designated as having "atypical CML" because their disease cannot be adequately described by the criteria for CMML or CML. The recent ability to more easily assess for mutations in clinical samples has led to the identification of alterations in genes that may be amenable to targeted therapy in the near future. Patients with disease that is caused by alterations other than *BCR-ABL* gene mutations are not expected to (and have been proven not to) respond to BCR-ABL-directed therapies such Gleevec, Sprycel, Tasigna, Bosulif or Iclusig. On rare occasions, mutations may be found in other genes that are also targeted by one or more of these TKIs.

See the free LLS publication *Chronic Myelomonocytic Leukemia (CMML)* and *Juvenile Myelomonocytic Leukemia (JMML)* for more information about these diseases.

Follow-up Care

Like the disease, CML follow-up care will vary from patient to patient. CML patients

- Will need to see their doctor on a regular basis: the doctor will evaluate the patient's health, blood cell counts and, possibly, bone marrow status.
- May have some tests repeated to see if they are benefiting from treatment and whether or not to continue it.
- 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
  - Diagnosis
  - All treatments
  - Names of drugs taken
  - Radiation treatment information
  - Surgery information
  - Transplant information
  - Information about any other treatments
  - Other medical history
  - Any other important information.

Normal Blood and 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 (coagulation factors); they are made by the liver.
  - Erythropoietin; it is made by the kidneys and stimulates red blood cell production.
  - Immunoglobulins. These are parts of cells that fight infection.
- Hormones, such as thyroid and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B_{12}
- Electrolytes, such as calcium, potassium and sodium.

Blood cells. The blood cells are suspended in the plasma. Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called "hematopoiesis." See Figure 6 on page 41.

Once the cell develops, it will develop into one of the three types of blood cells.

These are

1. Red blood cells (the cells that carry oxygen); they

- Make up a little less than half of the body's total blood volume
- Are filled with hemoglobin, which
  - Is the protein that picks up oxygen from the lungs and takes it around the body
  - Binds with carbon dioxide (CO_2) and removes it from the cells and then brings it back to the lungs. Then the CO_2 is removed when we exhale.

2. Platelets (cells that help blood to clot); they

- Are small cells (one-tenth the size of red blood cells)
- Help stop bleeding from an injury or cut
- Stick to the torn surface of the vessel, clump together, and plug up the bleeding site. They form a clot, with the help of proteins, such as fibrin, and electrolytes, such as calcium.

3. White blood cells (WBCs) (cells that fight infections). There are several types of WBCs, including

- Neutrophils and monocytes. These are "phagocytes" (eating cells). They eat bacteria and/or fungi and kill them. Unlike the red cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
- Eosinophils and basophils. These WBCs respond to allergens and/or parasites.
- Lymphocytes. These WBCs are mostly found in the lymph nodes, spleen and lymphatic channels. They are a key part of the immune system. Some enter the bloodstream. There are three major types of lymphocytes. They are
  - T lymphocytes (T cells)
  - B lymphocytes (B cells)
  - Natural killer (NK) cells.

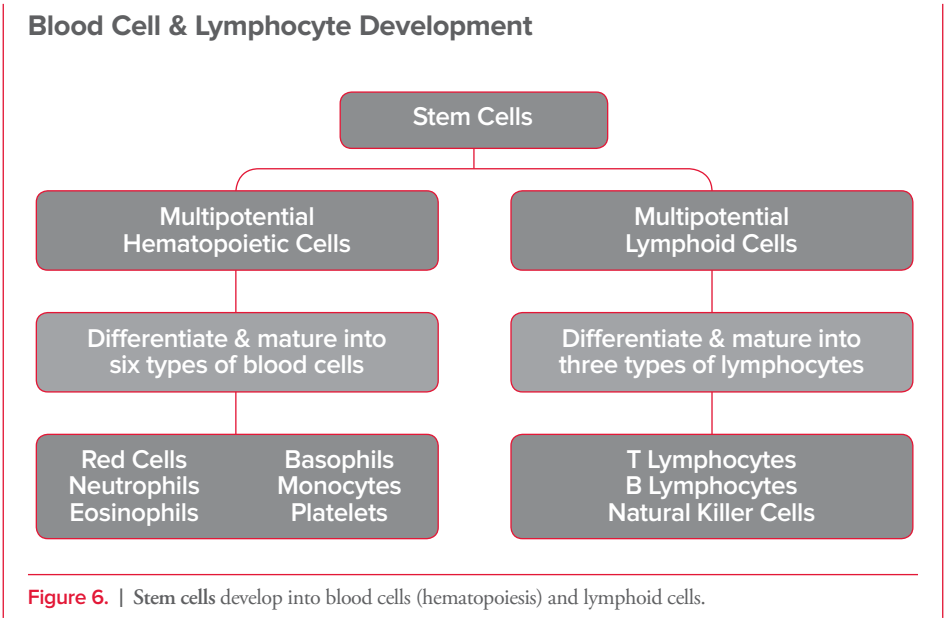


Figure 6. | **Stem cells** develop into blood cells (hematopoiesis) and lymphoid cells.

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

In babies, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have blood-forming marrow. In adults, it is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull.

Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be transplanted. Some stem cells (not many) enter the bloodstream and circulate; there are not enough of them to be counted in standard blood tests. Doctors know how to stimulate the growth of these cells in the marrow and have them migrate into the bloodstream. Then, a special technique called "apheresis" is used to separate them from the circulating blood so that they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

Health Terms

For definitions of words you do not see in this section, visit www.LLS.org/glossary.

ABL. A gene that is associated with chronic myeloid leukemia (CML). It is located on chromosome 9 and is mutated by the translocation (switching places) of a piece of chromosome 9 to chromosome 22. The mutation (change) of this gene causes CML and some cases of 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 marrow function and blood cells. It uses high dosages of chemotherapy and sometimes radiation to "turn off" a patient's immune system so that the donor cells are not rejected. See the free LLS publication, *Blood and Marrow Stem Cell Transplantation.*

Anemia. A health condition that occurs when a person has a low number of red blood cells and therefore a low hemoglobin concentration. When this happens, the blood carries less oxygen. People with severe anemia can be pale, weak, tired, and become short of breath. See Hematocrit.

Antibodies. Proteins released by plasma cells (derived from B lymphocytes) that recognize and bind to the specific foreign substances called "antigens." Antibodies coat, mark for destruction or inactivate foreign particles, such as bacteria, viruses or harmful toxins. Antibodies can be produced in the lab. Antibodies that specifically target a certain antigen are used in tests to identify types of cancer. Other antibodies attach to antigens on cancer cells and these have treatment applications.

Antigen. A foreign substance, mostly a protein, that creates an immune response when it is eaten, inhaled, or comes into contact with the skin or mucous membranes. Examples are bacteria, viruses and allergens. Antigens stimulate plasma cells to produce antibodies.

Antioncogene. See Tumor Suppressor Gene.

Apheresis. A process using a machine to take out the needed parts of the donor's blood and then 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. See Platelet Transfusion.

Autologous Stem Cell Transplantation. A treatment that uses a patient's own stem cells to slow the growth of certain blood cancers. See the free LLS publication, *Blood and Marrow Stem Cell Transplantation*.

Autosomes. See Karyotype.

Banding of Chromosomes. The staining of chromosomes with dyes that highlight bands or regions on the chromosome. The bands give the chromosomes more specific features, allowing individual distinctions to be made among them. This technique permits more precise identification of chromosomes. See Fluorescence In Situ Hybridization.

Basophil. A type of white blood cell present in certain allergic reactions.

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

Bilirubin. A brownish yellow substance that is produced mainly when the liver breaks down old red cells. It can be measured in a blood sample.

Blast Cells. A young (or immature) type of cell in the bone marrow. In healthy people, blast cells make up 5 percent or less of normally developing marrow cells.

Bone Marrow. A spongy tissue in the hollow central cavity of the bones where blood cells are made. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. In adults, the bones of the hands, feet, legs and arms no longer contain blood-forming marrow—these bones are filled with fat cells. 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 to find abnormal marrow cells. The area around the hip bone is numbed and then a special needle is inserted and a marrow sample (fluid) is drawn out. Usually this test is done at the same time as a bone marrow biopsy.

Bone Marrow Biopsy. A test to find abnormal marrow cells. The area around the hip bone is numbed and then a special needle is inserted and a piece of bone containing marrow is withdrawn. Usually this test is done at the same time as a bone marrow aspiration.

Bone Marrow Transplantation. See Allogeneic Stem Cell Transplantation; Autologous Stem Cell Transplantation.

Central Line (Indwelling Catheter). A special tube put into a large vein in the patient's upper chest. It is used to give medications, fluids or blood products or to take blood samples. See Port.

Chemotherapy. A treatment that uses medicine (chemical agents) to kill cancer cells.

Chromosome. Threadlike structures within cells that carry genes in a linear order. Human cells have 23 pairs of chromosomes: chromosome pairs 1 to 22 and one pair of sex chromosomes (XX for females and XY for males). See Translocation.

Colony-Stimulating Factor. See Growth Factor.

Computed Tomography (CT) Scan. A special procedure that uses x-rays to take pictures inside a person's body.

Cord-Blood Stem Cells. Stem cells that are present in blood drained from the placenta and umbilical cord (the link that attaches a mom to a new baby). These stem cells have the capability to repopulate the marrow of a compatible recipient and produce blood cells. Frozen cord blood is a source of donor stem cells for transplantation to HLA-matched recipients. Most cord-blood transplants are given by either matched or nearly matched unrelated donors.

Cytogenetic Analysis. A test that looks at the number and size of the chromosomes in cells. It is often used in cancer treatment and to see changes in the cells before and after treatment.

Cytogeneticist. A health care expert who uses special types of tests to look at cells and chromosomes.

Differentiation. When stem cells develop and mature and take on a new function. Stem cells will either 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.

Eosinophil. A white blood cell that helps to fight some parasitic infections and participates in allergic responses.

Erythrocytes. See Red Blood Cells.

Flow Cytometry. A test that finds specific cell types within a cell sample. The test may be used to examine blood cells, marrow cells or cells from a biopsy. A diluted suspension of cells from one of these sources can be tagged with an antibody specific for a site on the cell surface. The antibody has a chemical attached that will emit light when activated by a laser beam. The cells flow through the instrument called a "flow cytometer"; when the cells pass through its laser beam, those with the antibody-specific surface feature light up and then can be counted.

Fluorescence In Situ Hybridization (FISH). A technique used to study chromosomes in tissue. It uses probes with fluorescent molecules that emit light of different wavelengths and colors. Both *BCR* and *ABL* are labeled with chemicals that each release a different color. The color shows 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.

Germ Cell Mutation. A mutated cell in the egg or the sperm is passed from parent(s) to offspring. See Mutation.

Graft-Versus-Host Disease. The immune attack by lymphocytes in a donor's marrow or blood cell suspension (the graft) against the tissues of the recipient (the host). The immune cells most engaged in this reaction are the T lymphocytes present in the donor's blood or marrow, the source of the stem cells. The principal sites of injury to the patient are the skin, the liver and the gastrointestinal tract. The reaction does not occur in identical-twin transplants. The reaction may be minimal in closely matched individuals or severe in less well-matched individuals. See HLA.

Graft-Versus-Tumor Effect (Graft-Versus-Leukemia Effect). The potential immune reaction by which transplanted (donor) T lymphocytes recognize and attack the malignant cells of the recipient (host). This effect was noted when

- Disease recurrence after transplant was seen to be more likely if the donor and recipient were identical twins than if they were nonidentical siblings
- Disease recurrence was less likely the more pronounced the graft-versus-host disease (GVHD)
- The removal of donor T lymphocytes decreased the incidence of GVHD but also resulted in a higher frequency of disease relapse.

Each of these observations could be explained best as an immune attack by donor T lymphocytes against recipient tumor cells that, along with the intensive conditioning treatment, serves to keep the disease in check. This effect seems to be most active in patients who have some type of myeloid leukemia, although it may also occur in patients with other blood cancers. See HLA.

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

Granulocytic Sarcoma. A localized tumor of leukemic cancer cells. These tumors are found outside the marrow, may occur beneath the skin or other places, and may be the first sign of leukemia.

Granulocytosis. An increase above normal of the concentration of blood leukocytes (white cells)—specifically, granulocytes (neutrophils, eosinophils and basophils). This excludes lymphocytes and monocytes.

Growth Factor. A substance used to increase the numbers of neutrophils after chemotherapy. Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are growth factors that can be made in the lab.

GVHD. See Graft-Versus-Host Disease.

Hasford Scoring System. A scoring system that estimates survival of patients with chronic myeloid leukemia. The system designates patients as low-risk, intermediate-risk or high-risk. Scores are based on diagnostic markers, such as

- The size of the spleen
- Blood platelet count
- Patient age
- Blast cell count as well as the numbers of eosinophils and basophils circulating in the peripheral blood.

The Hasford scoring system may be less predictive in the tyrosine kinase inhibitor era; however, it does predict the probability of achieving a response to these drugs.

Hemapheresis. See Apheresis.

Hematocrit. The portion of the blood occupied by red blood cells. Normal amounts are 40 to 54 percent in males and 35 to 47 percent in females. Anemia occurs when the hematocrit level is below normal; erythrocytosis occurs when the hematocrit level is above normal.

Hematologist. A doctor who specializes in blood cell diseases.

Hematopathologist. A doctor or scientist who studies the blood cells and blood tissues to identify disease.

Hematopoiesis. The formation of all types of blood cells that starts in the marrow. For the blood cell development process, see *Normal Blood and Marrow* on page 39.

HLA. Human leukocyte-associated antigen. Proteins on the outer part of the cells that help fight illness. HLAs are passed from parents to their children and one in four siblings has the same type of HLA.

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.

Immunophenotyping. A process used to find specific types of cells within a blood sample. It looks at antigens or markers on the surface of the cell to identify antibodies.

Immunotherapy. A treatment that uses the body's immune system to treat diseases. Such therapies include

- Monoclonal antibody therapy—a type of drug using antibodies designed to attack specific parts of the cancer cells
- Radioimmunotherapy—a type of drug that uses radioactive substances and antibodies to attack cancer cells
- Vaccine therapy—drugs used to stimulate the immune system to fight cancer cells.

Karyotype. The order, number and appearance of chromosomes within a cell. Chromosomes are arranged in pairs. There are 23 pairs of chromosomes—22 pairs of numbered chromosomes, called "autosomes," and one pair of sex chromosomes, (either XX or XY). See Fluorescence In Situ Hybridization.

Leukocyte Alkaline Phosphate (LAP). A test that measures the amount of a certain enzyme (alkaline phosphatase) in white blood cells. People with certain types of blood cancer often have low LAP levels.

Leukocytes. See White Blood Cells.

Leukocytosis. An increase above the upper limit of normal in the concentration of blood leukocytes (white blood cells).

Leukopenia. A decrease below normal in the number of leukocytes (white blood cells) in the blood.

Lymph Nodes. Small oval-shaped organs found throughout the body. They are part of the lymphatic system and can become enlarged when someone has an infection or cancer.

Lymphocyte. A type of white cell important to the body's immune system. There are three major types of lymphocytes

- B lymphocytes, which produce antibodies to fight bacteria, viruses and fungi
- T lymphocytes, which have several functions, including helping assisting B lymphocytes to make antibodies
- Natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Macrophage. A monocyte in action (this is called a "scavenger cell"). When monocytes leave the blood and enter the tissue, they are known as "macrophages." Macrophages fight infection, eat dead cells and help lymphocytes with their immunity functions. See Monocyte/Macrophage.

Magnetic Resonance Imaging (MRI). A test that uses magnetic fields and radio waves to create images of the body's organs and tissues.

Maturation. See Hematopoiesis.

Minimal Residual Disease (MRD). The small number of cancer cells that may remain after treatment, even when the blood and marrow findings appear normal. These cells are only identified by sensitive molecular testing techniques.

Molecular Targeted Therapy. See Tyrosine Kinase Inhibitor (TKI).

Monocyte/Macrophage. A type of white blood cell that represents about 5 to 10 percent of the cells in normal human blood.

Multidrug Resistance. A cell characteristic that makes cells resistant to certain types of drugs.

Mutation. A change in the DNA that makes up a gene.

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

Neutropenia. An abnormal decrease in the number of neutrophils, a type of white blood cell, in the blood.

Neutrophil. A type of white blood cell and the main type that works to fight infection. People with some blood cancers, or those who have received treatment (such as chemotherapy) for cancer, 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 is the cause of a 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 cancer doctor.

Pancytopenia. A health condition when there is a decrease in the numbers of the three major blood cell types: red blood cells, white blood cells and platelets.

Pathologist. A doctor who finds disease by examining body tissue and fluids.

Petechiae. Pinhead-sized sites of bleeding in the skin that occur when someone has a low platelet count. They are often seen on the legs, feet, trunk and arms. Petechiae turn from red to brown, and eventually disappear. They stop developing when the platelet count increases.

Phagocytes. Cells that protect the body from infection by eating and killing microorganisms such as bacteria and fungi. The two main types 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 marrow and blood cells of patients with chronic myeloid leukemia and of some patients with acute lymphoblastic leukemia. The abnormality, a shortening of the long arm of this chromosome, was first observed and reported by doctors at the University of Pennsylvania in Philadelphia; thus the name "Philadelphia chromosome." In most cases, the lost piece of chromosome 22 sticks (translocates) to chromosome 9. Indeed, some of chromosome 9 also sticks

(translocates) to chromosome 22. This circumstance is referred to as a "balanced translocation," because virtually equal lengths of partial chromosome arms exchange position. Because chromosome 22 is a very short chromosome and chromosome 9 is a very long one, the lengthening of chromosome 9 was less apparent than the shortening of 22 until more sensitive detection techniques became available. The abnormality of chromosome 22 is now usually abbreviated as "Ph chromosome."

Platelets. Also known as "thrombocytes," platelets are small colorless blood cells. They migrate to 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.

Platelet Transfusion. This procedure transfers blood platelets from one patient to another. About six single-unit blood donors are often needed to provide enough platelets to raise the patient's platelet level. Platelet transfusions may help some CML patients. For more information, see the free LLS publication *Blood Transfusion*. See HLA; Apheresis.

Polymerase Chain Reaction (PCR). A technique to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be studied or determined. This technique has become useful in detecting a very low concentration of residual blood cancer cells, too few to be seen using a microscope. PCR can detect the presence of one blood cancer cell among 500,000 to one million blood cancer cells. PCR requires a specific DNA (or RNA) abnormality or marker, such as an oncogene, in cancer cells to be used for identifying residual abnormal cells.

Port. A small device placed under the skin and attached to a central line or a peripherally inserted central catheter (PICC or PIC line). It permits access to the line. Medicines and nutrition can be administered and blood samples can be withdrawn via a port.

Promyelocyte. A cell that forms during its transition from an immature cell to a mature cell, a part of the development cycle for certain types of white blood cells.

Red Blood Cells. Blood cells (erythrocytes) contain 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. Patients receive lower dosages of chemotherapy drugs and/or radiation to prepare for a reduced-intensity transplant. 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. A disease that does not go away or improve much after initial treatment.

Relapse/Recurrence. A return of the disease after it has been in remission following therapy.

Remission. When signs of a disease disappear. This usually follows treatment.

Resistance to Treatment. When cancer cells continue to grow even after administration of strong drugs and/or treatments.

Scavenger Cell. See Monocyte/Macrophage.

Sokal Scoring System. A scoring system used for patients with chronic myeloid leukemia that estimates their survival. Patients are rated low risk, intermediate, or high risk based on their spleen size, platelet count, age and blast count. It is also used to predict the response to tyrosine kinase inhibitors (TKIs). TKIs are a type of drug used to treat CML.

Somatic Cell Mutation. A change in the DNA that occurs in a specific tissue cell which may result in a tumor. Most cancers start after a somatic cell mutation.

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.

Splenectomy. Surgical removal of the spleen.

Splenomegaly. Enlargement of the spleen.

Stem Cell Transplantation. See Allogeneic Stem Cell Transplantation; Autologous Stem Cell Transplantation.

Stem Cells. Primitive marrow cells that mature into red blood, white blood cells, and blood platelets. Stem cells are mostly found in the marrow, but some leave and circulate in the bloodstream. Stem cells can be collected, preserved, and used for stem cell therapy. See Hematopoiesis.

Thrombocyte. A synonym for "platelet."

Thrombocythemia. A disorder characterized by too many platelets in the blood.

Thrombocytopenia. A disorder characterized by too few platelets in the blood.

Translocation. An abnormality of chromosomes in marrow or lymph node cells that occurs when a piece of one chromosome breaks off and attaches to the end of another chromosome. In a balanced translocation, genetic material is exchanged between two different chromosomes with no gain or loss of genetic information. When a translocation takes place, the gene at which the break occurs is altered. See Mutation.

Tumor Suppressor Gene (Antioncogene). A gene that works to stop cell growth.

Tyrosine Kinase. A type of enzyme that plays a key role in cell function. It is normally present in cells, and a normal gene, *ABL* on chromosome 9, directs its production. In chronic myeloid leukemia, an alteration in the DNA results in a mutant fusion gene, *BCR-ABL*, which produces an abnormal or mutant tyrosine kinase. This abnormal enzyme leads to a cascade of effects in the cell that transforms it into a leukemic cell.

Tyrosine Kinase Inhibitor (TKI). A type of drug, which includes widely used imatinib mesylate (Gleevec®). These drugs block the effects of the mutant BCR-ABL tyrosine kinase found in CML. 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. Dasatinib (Sprycel®) and nilotinib (Tasigna®) are second-generation TKIs. They are being used either as initial treatment or after therapy when patients prove resistant to or cannot tolerate Gleevec. Bosutinib (Bosulif®) is approved for patients with resistance to Gleevec and other TKIs, and ponatinib (Iclusig) is approved for patients with the drug-resistant T315I mutation as well as patients without other TKI options.

White Blood Cells. Also known as "leukocytes," the five types of infection-fighting cells in the blood. These are neutrophils, eosinophils, basophils, monocytes and lymphocytes.

More Information

Free LLS publications include

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

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

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