# Chronic Myelogenous Leukemia

LEUKEMIA | LYMPHOMA | MYELOMA

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NOVARTIS ONCOLOGY

The Leukemia & Lymphoma Society®

*Fighting Blood Cancers*

# Table of Contents

# Introduction

This booklet about chronic myelogenous leukemia is for patients and their families. A glossary is provided at the end of the booklet to aid readers with understanding medical terms. We hope the booklet is helpful. We welcome comments about its clarity as well as suggestions for any information that would be useful to include in future editions.

The booklet begins with a brief description of normal blood and marrow. A description of the disease and its management follows.

# Normal Blood and Marrow

Blood is composed of plasma and cells suspended in plasma. The plasma is largely made up of water in which many chemicals are dissolved. These chemicals include:

- Proteins (such as albumin)
- Hormones (such as thyroid hormone)
- Minerals (such as iron)
- Vitamins (such as folate)
- Antibodies, including those developed by the body from vaccinations (such as poliovirus antibodies).

The cells suspended in plasma include red cells, platelets and white cells (neutrophils, eosinophils, basophils, monocytes and lymphocytes).

- The red cells make up half the volume of the blood. They are filled with hemoglobin, a protein that picks up oxygen in the lungs and delivers oxygen to the cells all around the body.
- The platelets are small cells (one-tenth the size of red cells) that help stop bleeding at the site of an injury in the body. For example, when an individual has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the blood vessel, clump together and plug up the bleeding site. Later, a firm clot forms. The blood vessel wall then heals at the site of the clot and returns to normal.
- White cells are key parts of the immune system.
- Neutrophils and monocytes are called “phagocytes” (eating cells). Unlike red cells and platelets, these white cells leave the blood and enter the tissues, where they can ingest and kill invading bacteria or fungi and help combat infection.
- Eosinophils and basophils are two additional types of white cells that respond to allergens (allergy-causing substances).
- Most lymphocytes, another type of white cell, are found in the lymph nodes, the spleen, and lymphatic channels, but some enter the blood. There are three major types of lymphocytes: T cells, B cells and natural killer cells.

Marrow is a spongy tissue where blood cell development takes place. It occupies the central cavity of bones. In newborns, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms, and legs no longer have functioning marrow. The spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull contain the marrow that makes blood cells in adults. Blood passes through the marrow and picks up formed red and white cells and platelets, for circulation throughout the body.

The process of blood cell formation is called hematopoiesis. A small group of cells called "stem cells" develop into all the blood cells in the marrow by the process of differentiation (see Figure 1).

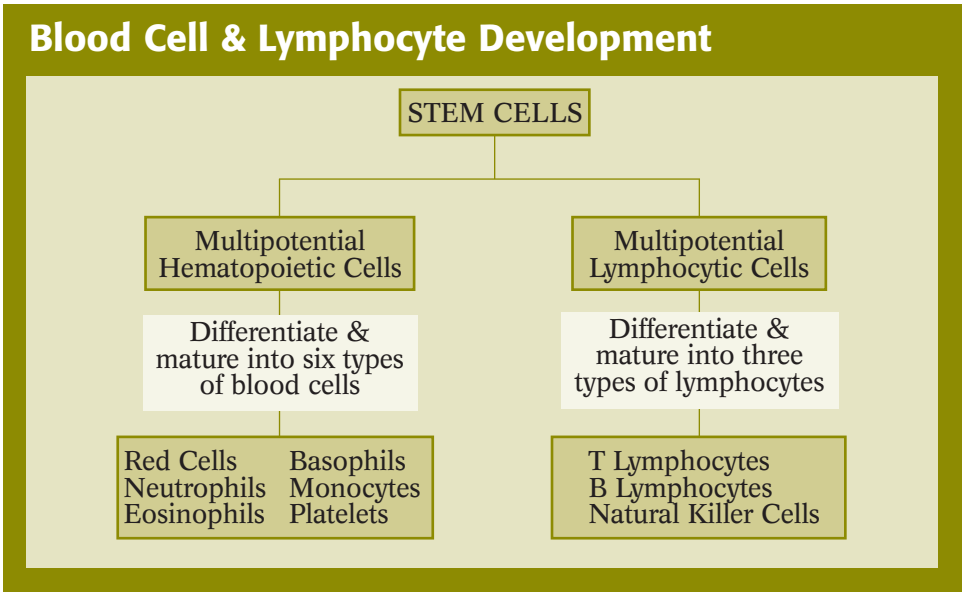



Figure 1. Stem cells develop into blood cells (hematopoiesis) and lymphatic cells.

When the fully developed and functional cells are formed, they leave the marrow and enter the blood. In healthy individuals there are enough stem cells to keep producing new blood cells continuously.

Some stem cells enter the blood and circulate. They are present in such small numbers that they cannot be counted or identified by standard blood count tests. Their presence in the blood is important because they can be collected by a special technique called "hemapheresis." If enough stem cells are collected from a compatible donor they can be transplanted to a recipient.

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

**Summary** Blood cells are made in the marrow. When the cells are formed and functional, they leave the marrow and enter the blood. The red cells and the platelets carry out their respective functions of delivering oxygen and plugging up injured blood vessels throughout the body. The white cells (neutrophils, eosinophils, basophils, monocytes and lymphocytes) enter the tissues (for example, the lungs) to combat infections, such as pneumonia, and perform other immune functions.

# Leukemia

European physicians in the 19th century were the earliest observers of patients who had markedly increased white cell counts. The term "Weisses Blut" or "white blood" emerged as a designation for the disorder. Later, the term "leukemia" (derived from the Greek words "leukos," meaning "white," and "haima," meaning "blood") was used to indicate the disease.

The major forms of leukemia are divided into four categories. The terms "myelogenous" and "lymphocytic" denote the type of white cell involved. Myelogenous and lymphocytic leukemias each have acute and chronic forms. Thus, the four major types of leukemia are: acute or chronic myelogenous leukemia (CML), and acute or chronic lymphocytic leukemia.

Acute leukemia is a rapidly progressing disease that primarily affects cells that are not fully developed or differentiated. These immature cells cannot carry out their normal functions. Chronic leukemia progresses slowly and permits the growth of greater numbers of developed cells. In general, these mature cells can carry out some of their normal functions.

The ability to measure specific features of cells (including appearance, chromosome and gene abnormalities, and immune characteristics) has led to further subclassification of the major categories of leukemia. The categories and subsets allow physicians to determine how quickly the disease may progress and to decide what treatment may work best for a given form of the disease.

# Chronic Myelogenous Leukemia

CML is called by several names, including chronic granulocytic, chronic myelocytic or chronic myeloid leukemia. CML results from a change to the DNA of a stem cell in the marrow. Scientists do not yet understand what produces this change in the DNA, which is not present at birth.

The stem cell's changed DNA gives the malignant (cancerous) cell a growth and survival advantage over a normal stem cell. The resulting uncontrolled growth of white cells, if left untreated, will lead to a massive increase in their concentration in the blood. CML does not completely interfere with the development of mature red cells, white cells and platelets; these cells can generally continue to function normally. This is an important distinction from acute leukemia and accounts for the less severe early course of chronic leukemias.

## Incidence

About 4,500 new cases of CML were diagnosed in the United States in 2006. Most cases of CML occur in adults, but children may develop the disease. The course of the disease in children is similar to that in adults. However, the outcome of treatment with stem cell transplantation is better in younger individuals. (See information about stem cell transplantation in the **Treatment** section.)

**Chronic Myelogenous Leukemia**
**Age-Specific Incidence Rates 2000-2003**

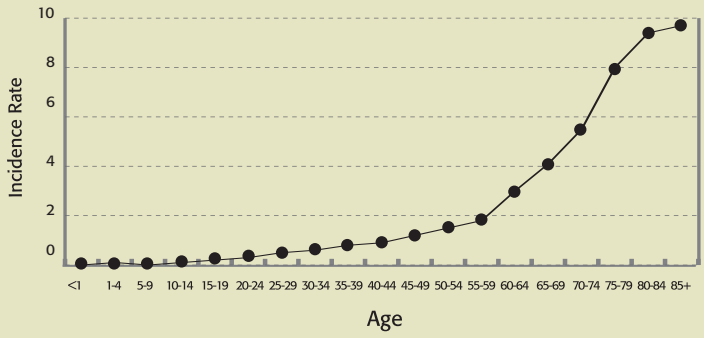



Figure 2. The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of CML per 100,000 in a given age-group. (Data: Surveillance, Epidemiology, and End Results [SEER] Program of the National Cancer Institute [NCI] 2006, *Cancer Statistics Review, 2000-2003.*)

Childhood cases (patients under 20 years of age) represent about 2.8 percent of all CML patients. The frequency of the disease increases with age, from about less than one in 100,000 until about age 40, to nearly 2 in 100,000 at age 55, to about one in 10,000 people at age 80 and older (see Figure 2).

## Causes and Risk Factors

In 1960, two physicians studying chromosomes in cancer cells noticed that one chromosome in cells from patients with CML (chromosome 22) was shorter than the same chromosome in normal cells. They named this shortened chromosome 22 the "Philadelphia chromosome," because the observation was made in Philadelphia at the University of Pennsylvania School of Medicine. It is now referred to as the "Ph chromosome" (see Figure 3). Thus, CML is distinguished from other leukemias by the presence of a genetic abnormality of chromosome 22 in leukemic cells.

### Marrow Cell Chromosomes

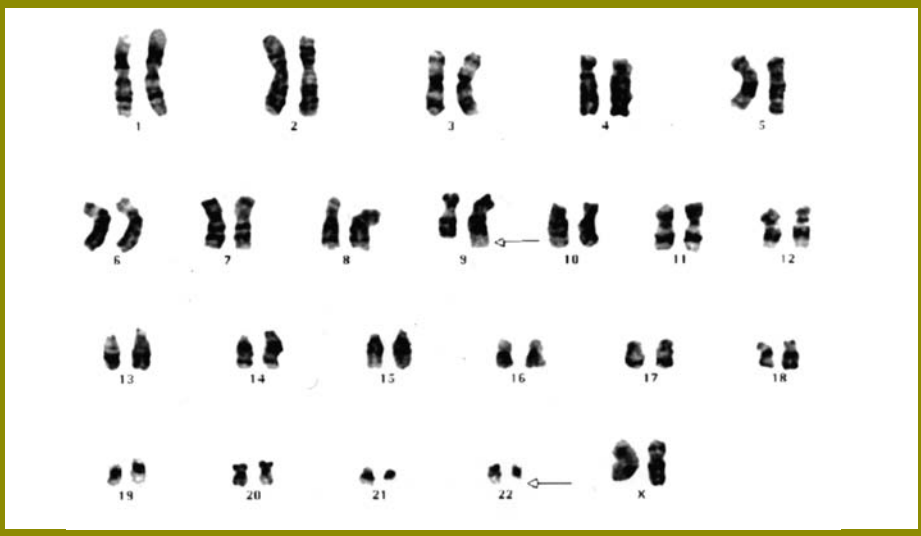



Figure 3. This figure shows the set of chromosomes from a marrow cell of a female patient with CML. The total number of chromosomes (46) is normal, consisting of pairs of chromosomes 1 through 22 and the sex chromosomes (in this instance, two X chromosomes for a female). The higher the chromosome number, the smaller the chromosome. The lower arrow indicates the shortened arm of chromosome 22 (the Ph chromosome), characteristic of the leukemic marrow cells of patients with CML. The upper arrow 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, Ph.D., University of Rochester Medical Center, Rochester, NY.*

Normal human cells have 46 chromosomes, composed of 22 pairs of chromosomes and two sex chromosomes. The first 22 pairs (numbered 1 through 22) are called autosomes. The 45th and 46th chromosomes consist of sex-determining chromosomes, either XY in males or XX in females.

Further studies established that two chromosomes, usually chromosomes number 9 and 22, were abnormal. Pieces of the chromosomes, which are broken off in the leukemic cells of patients with CML, switch with each other. The detached portion of chromosome 9 sticks to the broken end of chromosome 22, and the detached portion of chromosome 22 sticks to the broken end of chromosome 9. This abnormal exchange of parts of chromosomes is called a translocation. This translocation of chromosome pieces occurs only in the damaged stem cell and in the various blood cells derived from that stem cell. The chromosomes of the cells in other tissues are normal.

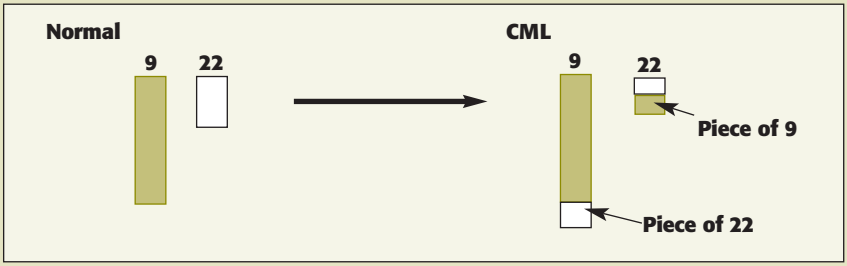
The breakage on chromosome 9 disrupts a gene referred to as "ABL" (for Abelson, the scientist who first described this gene). The breakage on chromosome 22 involves a gene referred to as "BCR" (for breakpoint cluster region). The human ABL gene is mutated by the breakage of chromosome 9. The mutated gene is translocated to chromosome 22 and fuses with the remaining part of the BCR gene. This fusion between BCR and ABL leads to an abnormal fused gene, called "BCR-ABL."

The function of a gene is to direct the production of a protein in the cell. In CML, the ABL gene fuses to the BCR gene, resulting in the production of an elongated enzyme protein called "tyrosine kinase." This elongated protein functions abnormally and leads to dysfunctional regulation of cell growth and survival. The abnormal protein resulting from the mutant BCR-ABL gene is responsible for the development of the disease (see Figure 4 and Figure 5). Tyrosine kinase is a target for specific drug treatment that may block its effects (see **Treatment** section).

The cause of the chromosomal breakage, occurring in nearly all CML patients, is not known, for the most part. However, in a small number of patients, exposure to very high doses of radiation causes the breakage. This effect has been most carefully studied in the Japanese survivors of the atomic bomb, whose future risk of developing leukemia was significantly increased. A slight increase in risk also occurs in some individuals treated with high-dose radiotherapy for other cancers, such as lymphoma. Exposures to diagnostic dental or medical x-rays have not been associated with an increased risk of CML.

## Leukemia-Causing Event in a Marrow Stem Cell

**Translocation of chromosomes 9 and 22**




- **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 tyrosine kinase (see Figure 5).**
- **The abnormal enzyme protein is the principal factor in converting the marrow stem cell from a normal cell into a leukemic cell.**

Figure 4. The process of translocation between the genes on chromosome 9 and chromosome 22.

## Symptoms and Signs

The onset of CML is associated with symptoms that usually develop gradually. Most patients feel a loss of well-being. They tire more easily and may feel short of breath during physical activity. They may have a pale complexion from anemia (a decrease in red cells). Discomfort from an enlarged spleen may be present on the left side of the abdomen. Patients may experience excessive sweating, weight loss and inability to tolerate warm temperatures. For people who have access to periodic health examinations, CML may be discovered as a result of blood tests given in the course of periodic medical examinations.

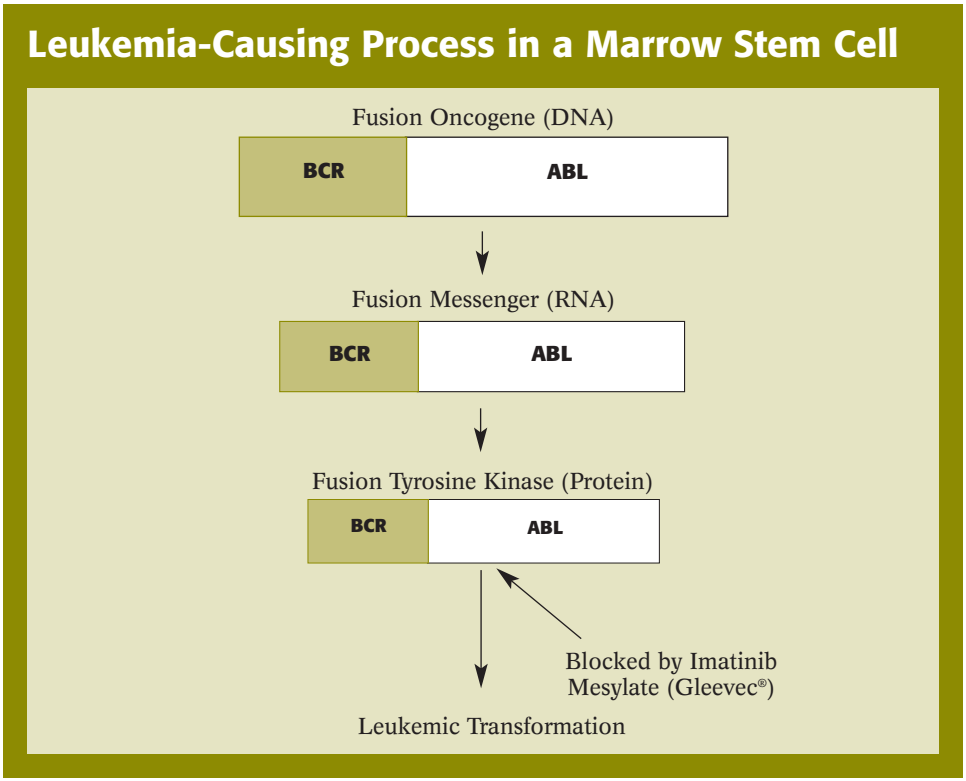



Figure 5. The mutant gene (oncogene) shown on the top bar is caused by the fusion of the ABL gene from chromosome 9 and the BCR gene from chromosome 22. The gene's DNA sequence is copied into messenger RNA, shown in the middle bar. The messenger RNA causes the formation of a mutant protein, an enzyme 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 cell counts and low red cell counts. Several BCR-ABL inhibitors including imatinib mesylate (Gleevec®), dasatinib (Sprycel™) and nilotinib (Tasigna™) can bind to the mutant protein, blocking its effects. This action is referred to as "oncoprotein-targeted therapy" because of the specific drug action on the protein that induces the leukemia (see **Treatment** section).

## Diagnosis

There are several tests that examine blood and marrow cells to diagnose CML.

**Complete Blood Count** This is a test that measures the number and type of cells in blood. In most cases, blood and marrow cells are examined to diagnose CML. With this disease, the hemoglobin concentration is decreased and the white cell count is increased, often to very high levels. Examination of stained (dyed) blood cells with a light microscope shows a characteristic pattern of white cells: a small proportion of very immature cells (leukemic blast cells and promyelocytes) and a larger proportion of maturing and fully matured white cells (myelocytes and neutrophils). Blast cells, promyelocytes and myelocytes are not present in the blood of healthy individuals.

**Cytogenetic Analysis** This test measures the number and structure of the chromosomes. A sample of marrow is examined to confirm the blood-test findings and to determine if there is a chromosomal abnormality. The presence of the Ph chromosome (a shortened chromosome number 22) in the marrow cells, a high white cell count and other characteristic blood and marrow test findings confirm the diagnosis of CML.

A small percentage of patients with clinical manifestations of CML do not have a cytogenetically detectable Ph chromosome but are positive for the BCR rearrangement on chromosome 22.

There are other techinques that can detect the chromosome abnormalities that characterize CML.

**Fluorescence (F) in (I) situ (S) hybridization (H)** Often referred to as FISH, this is another method used to identify cells in which the nucleus contains chromosomes that have the 9;22 translocation characteristic of CML. This method is shown in Figure 6. FISH uses DNA-binding agents that are specific for the pieces of DNA of interest, in this case the ABL and BCR genes.

The probe for BCR and for ABL can be labeled with chemicals that release a different color of light. The color can be localized to the chromosome on which the gene is present, normally chromosome 9 for ABL and chromosome 22 for BCR. This permits the translocated piece of chromosome 9 to be seen in its abnormal position on chromosome 22, as shown in Figure 6. This chromosome test for CML is more sensitive than standard cytogenetics that identify the Ph chromosome. In addition,

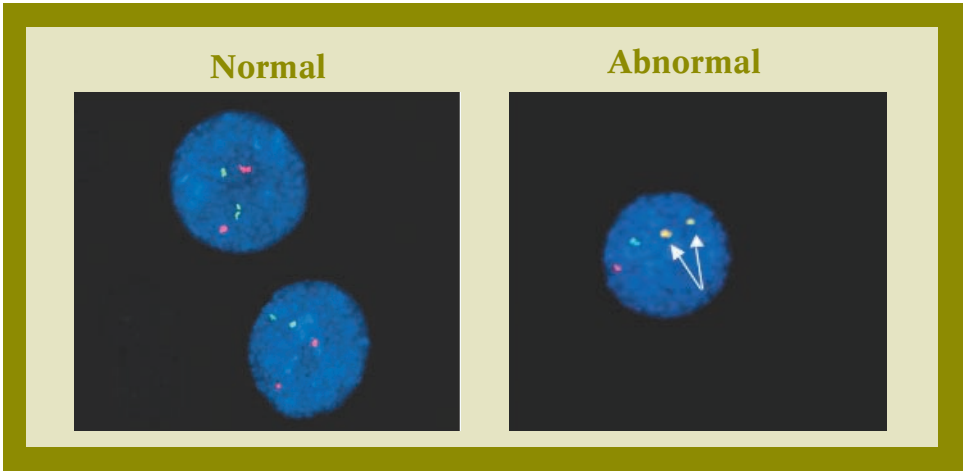



Figure 6. *Fluorescence in situ hybridization,* or FISH, is a DNA-mapping technique that uses fluorescent molecules to mark the BCR-ABL gene in CML. In normal cells, two red and two green signals indicate the location of the normal ABL and BCR genes, respectively. In abnormal cells, the BCR-ABL fusion is visualized through the fusion of the red and green signals, which is frequently detected as a yellow fluorescence (noted by arrows).

FISH can detect the abnormality in blood cells and does not require a marrow examination. For that reason, it is also useful for following the effects of CML treatment; it can determine whether a considerable number of CML cells have decreased in the blood.

**Polymerase Chain Reaction (PCR) Test** This is a sensitive test of blood cells. The PCR can increase small amounts of specific pieces of either RNA or DNA to make them easier to detect. Thus, the alteration in DNA caused by the chromosome breakage in CML can be detected. This testing method is more sensitive than FISH and can detect one BCR-ABL-positive cell in a background of about 500,000 normal cells. Quantitative PCR is used to determine the amount of BCR-ABL in the blood. This test is also used to quantify the decrease in the number of CML cells after therapy and to measure if CML cells are increasing in number during patient follow-up after treatment.

## Three Phases of CML

CML has three phases: 1) the chronic phase, 2) the accelerated phase and 3) the blast crisis phase.

**Chronic Phase** Most CML patients are diagnosed while in the chronic phase of the disease. During this phase, CML symptoms are less severe because CML cells can mature into functioning white cells and platelets. Thus, infection or bleeding complications do not occur in the chronic phase and if patients are treated — bringing their total white cell count down to near-normal levels — they can generally function in their usual ways. The improved white cell count is accompanied by shrinkage of the spleen, improvement in hemoglobin concentration and a return to feeling well.

**Accelerated Phase and Blast Crisis Phase** In the accelerated phase of CML, patients lose their response to treatment. Anemia may develop or progress; the white cell count may either fall to very low levels or rise because of accumulation of blast cells; platelet counts may decrease. The blast count increases in the blood in the accelerated phase and is further elevated in "blast crisis;" the spleen may become enlarged; the patient may lose his or her sense of well-being and other complications may follow.

During the blast crisis phase, the number of blast cells increases in marrow and blood to levels seen in acute leukemia; the red cell, platelet and neutrophil counts may decrease further; episodes of infection and bleeding may result. Symptoms such as fatigue, shortness of breath and abdominal pain as well as signs such as bone pain and spleen enlargement may occur. Blast crisis is similar to acute leukemia in its signs and its effects on the patient.

The progression from chronic phase, usually an easily controlled phase, to accelerated phase or blast crisis may result from additional genetic alterations in the leukemic stem cells. In some cases, additional chromosome abnormalities can be identified by cytogenetic analysis. In other cases, these genetic changes in the leukemic stem cells cannot be identified by laboratory tests currently available.

# Treatment

The treatments for CML are described in this section.

## Chronic Phase

Treatment in the chronic phase of CML usually returns the patient's blood cell counts to normal values and maintains them either at or close to normal levels for years. The size of the spleen decreases until it approaches its normal size. Infections and abnormal bleeding are unusual. Patients can resume their previous levels of day-to-day activities. However, they will need to receive periodic health checks, including blood counts and cytogenetic analyses of blood. Less frequently, they will need to have marrow examinations. Patients will also need to have their tolerances to drugs assessed and may need dosage adjustments.

Patients with CML begin treatment with imatinib, the standard initial therapy for chronic phase CML (see Table 1, page 16). Imatinib is a type of drug called a "BCR-ABL tyrosine kinase inhibitor." The goal in treating chronic phase CML is to restore the blood counts to normal levels and eliminate cells containing the BCR-ABL oncogene. For many patients, imatinib has kept the chronic phase of CML under control for over six years, the length of the observation period since this drug's introduction.

Imatinib is well tolerated by a majority of CML patients; tolerance is about the same for both younger and older individuals with CML. However, some patients either cannot tolerate therapeutic doses of imatinib or do not respond to imatinib. There are two second-generation BCR-ABL tyrosine kinase inhibitors available for these patients, dasatinib and nilotinib. These drugs inhibit the BCR-ABL oncoprotein, as does imatinib. However, they attach to the oncoprotein in different ways, making them effective for many patients who are imatinib-resistant. In addition, many patients who cannot tolerate imatinib are able to use dasatinib or nilotinib for treatment.

All of the BCR-ABL tyrosine kinase inhibitors are given by mouth. Dasatinib has been approved by the U.S. Food and Drug Administration (FDA). It is specifically indicated to treat adults with chronic, accelerated, or myeloid or lymphoid blast phase CML who have been shown to be either resistant to or intolerant of prior therapy including treatment with imatinib. Nilotinib is an experimental agent available in clinical trials for patients in all phases of CML.

Treatment with imatinib, dasatinib or nilotinib does not result in a cure; patients will relapse if they stop taking the drug; PCR testing shows that most of them still have evidence of residual CML cells. Nevertheless, evidence suggests that patients receiving these drugs may remain in remission for very long periods.

## Accelerated Phase or Blast Crisis Phase

The goal in treating accelerated or blast crisis phase CML is to destroy all cells that contain the BCR-ABL gene. If this is not possible, the goal is to return the disease to the chronic phase. High-dose imatinib and allogeneic stem cell transplantation (for patients of an appropriate age, in generally good health and who have an available stem cell donor) are the principal means of successful treatment. Dasatinib is another drug treatment option for imatinib-resistant patients who enter accelerated or blast crisis phase while on imatinib.

When stem cell transplantation is an option (see page 18), drug therapy is especially useful to induce a remission or restore patients to the chronic phase before they undergo transplant surgery. These patients are then better prepared physically to benefit from the procedure.

BCR-ABL tyrosine kinase inhibitor drugs have a lower frequency of severe side effects than optimal doses of interferon. However, interferon may be useful to treat patients who are either intolerant of or resistant to imatinib and dasatinib. Interferon given in optimal doses to older patients has a high frequency of side effects compared to its side-effect profile for younger patients. It often cannot be tolerated. It can induce flu-like side effects: fever, muscle aches and weakness. Some patients, those with prolonged fatigue and weight loss, for example, may need a reduction in the dose. Hair loss, diarrhea, depression, ulceration of the lining of the mouth, cardiac effects and other side effects occasionally occur.

## Response to Treatment

Measuring the response to therapy is of critical importance in managing treatment regimens for patients with CML. Most likely, the greater the response to drug therapy, the longer the patient's disease will be controlled. The degree of response is also an important factor – along with the age of the patient and other factors – influencing the decision to use allogeneic transplantation.

## Table 1. Some Drugs Used in the Treatment of the Chronic Phase of Chronic Myelogenous Leukemia

**Usual Initial Treatment**
Imatinib Mesylate (Gleevec®)

**Other Treatments***
Dasatinib* (Sprycel™)
Nilotinib** (Tasigna™)
Interferon-alpha (Roferon®-A, Intron® A)
Pegylated-interferon-alpha
Hydroxyurea (Hydrea®)
Cytarabine (Cytosar-U®)
Busulfan (Busulfex,® Myleran®)
Homoharringtonine

* **Used for patients intolerant/resistant to imatinib or in other special circumstances.**

** **Investigational drug.**

Table 1 lists drugs that have been used prior to the introduction of imatinib, now the first choice of treatment for chronic phase CML. Dasatinib has been approved for patients who cannot tolerate or do not respond to imatinib. Nilotinib is currently being tested in clinical trials for patients resistant or intolerant to imatinib. In special circumstances, interferon or other drugs listed may still be used to treat CML.

Response to treatment may be defined as hematologic, cytogenetic or molecular.

- In a **complete hematologic response**, the leukemia cell numbers are decreased; immature leukemic cells are largely eliminated from the blood; and the hemoglobin concentration, white cell count and platelet count are either at or near normal values.
- In a **complete cytogenetic response**, there are no cells in the marrow with the Ph chromosome and no cells in the blood that can be detected by FISH containing the BCR-ABL oncogene.
- In a **complete molecular response**, PCR testing reveals no evidence of the BCR-ABL oncogene-containing cells in the blood.

Most patients in chronic phase CML have a complete hematologic response on imatinib; a substantial proportion of these patients undergoing treatment with imatinib eventually achieve a complete cytogenetic response. Patients who have a complete cytogenetic response often have a partial molecular response; a smaller proportion of patients achieve a complete molecular response.

The response to imatinib is, in part, a function of the dose that can be tolerated by the patient and the length of time from initiation of the drug to the determination of response. Patients in the chronic phase of CML whose responses to the standard dose are not good have achieved a good response at higher doses. Studies are in progress to evaluate whether the standard starting dose of imatinib should be increased. Possibly, a larger starting dose (if it can be tolerated) may result in greater suppression of CML cells and a higher rate of cytogenetic and molecular remission.

In initial studies, dasatinib produced hematologic and cytogenetic responses in patients with CML who either cannot tolerate or are resistant to imatinib. Future studies are needed to evaluate dasatinib dose ranges.

**Side Effects of Imatinib and Dasatinib Therapy** Imatinib produces a variety of side effects, most of which can be managed without stopping the drug. The more common effects of imatinib include fluid retention, puffiness around the eyes, nausea and vomiting, muscle cramps, diarrhea and rash.

Limited data are available on the reproductive effects (if any) of imatinib. The manufacturer has indicated that women of childbearing age who are taking imatinib should use effective contraception and should not breastfeed while taking imatinib.

As more patients are treated with imatinib for longer periods, certain potentially toxic effects have been uncovered. Two adverse effects are

- Loss of bone minerals, which may lead ultimately to osteoporosis
- Cardiac effects resulting in heart failure (very uncommon).

These two problems should be manageable medically in most cases. The drug affects three types of tyrosine kinases that are critical to the function of normal cells. In most patients the principal effect of the drug is on the mutant protein, BCR-ABL tyrosine kinase, in CML cells. However, the possibility of effects on normal cells exists and may account for these and other side effects.

Results of initial studies indicate that treatment with dasatinib may lead to low white cell and platelet counts, collection of fluid in the chest (pleural effusion), diarrhea, headache, fluid accumulation (edema), low blood calcium levels and slight abnormalities in liver function test results.

## Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation is the only curative treatment for CML at this time. This therapy was formerly referred to as bone marrow transplantation. It is now possible to harvest stem cells from either peripheral or cord blood as well as from marrow. Allogeneic stem cell transplantation requires a tissue-type (HLA-matched) donor (related or unrelated) and is most successful in younger patients. However, patients up to about 60 years of age who have a matched-related or matched-unrelated donor may be considered for this treatment. The availability of an HLA-matched, related donor, usually a brother or sister or an HLA-matched, unrelated donor, can be determined by searching the National Marrow Donor Program database.

Allogeneic stem cell transplantation is effective in two ways. Initially, the transplant replaces the blood cell- and immune cell-forming capability of the patient. This capability is suppressed by the disease and further damaged by the very high-dose chemotherapy given to destroy residual CML cells prior to transplant. Secondly, the engrafted donor stem cells make immune cells that, although compatible with the major tissue-type determinants of the recipient, have incompatibility with the minor tissue-type determinants. (The minor tissue-type determinants are not matched as part of the compatibility testing before transplant.) These engrafted donor immune cells recognize the patient's minor tissue-type determinants on the CML cells and may attack and destroy those cells. This important reaction is called "graft versus leukemia effect."

Please see the **Clinical Trials** section for more information about other types of transplants under study.

Making the decision to use allogeneic transplantation has become more difficult as a result of the large proportion of patients who have a very good response to imatinib (and now also have the availability of other BCR-ABL tyrosine kinase inhibitors). On the one hand, transplant is the only treatment that can cure patients with CML. As such, allogeneic stem cell transplantation continues to be an important therapy for CML patients who have an HLA-matched donor. On the other hand, the BCR-ABL tyrosine kinase inhibitors may be able to control the disease for very long periods. Thus, several factors including the patient's age, the genetic compatibility of the prospective donor and the degree of the response to imatinib therapy will be weighed by patients and their physicians to determine if and when to use transplantation.

## Donor Lymphocyte Infusion

If a patient who has had an allogeneic stem cell transplant has a relapse of CML, he or she may be given an infusion of lymphocytes from the original stem cell donor. This may induce a more intense immune reaction against the patient's CML cells. This therapy has been used effectively in patients with CML who relapse after transplantation. One important side effect from such therapy is that the infused immune cells also recognize patient tissue-type determinants on other tissues and may engender a graft versus host reaction, which can be disabling. However, most patients derive a net benefit from such an infusion.

## Autologous Stem Cell Infusion

All patients do not have the key combination of younger age and an HLA-matched donor that makes allogeneic transplantation feasible. Thus, physicians are studying the use of the patient's own marrow or blood as a source of stem cells for transplantation. This treatment option is known as "autologous stem cell infusion." The patient's own marrow or blood stem cells are harvested and then frozen during the chronic phase of CML. Later, they are used to treat the patient if or when he or she enters the accelerated phase of the disease. The hope for this procedure is that restoring the chronic phase of the disease will lengthen the patient's life and lessen symptoms. In addition, special techniques can harvest largely normal stem cells during the chronic phase of the disease and could theoretically restore normal blood cell development after intensive drug therapy.

## Leukapheresis

Some patients may have extraordinary increases in their white cell counts at the time of diagnosis. This can impair blood flow to the brain, lungs, eyes and other sites. Patients can be treated initially with the removal of white cells by a machine that is similar to a dialysis machine. The process is called leukapheresis. Hydroxyurea, a drug that can decrease the white cell count, is often used as well. After the white cell count has been decreased, treatment with imatinib can be started.

Leukapheresis can be used if the disease occurs during the first months of pregnancy, when chemotherapy may be harmful to fetal development.

## Acute Transformation of Chronic Phase

The final progression of CML resembles acute leukemia. This is referred to as blast crisis. During this phase, the leukemic blast cells dominate the marrow and blood. In about one-quarter of patients, the transformation takes on the appearance of acute lymphocytic leukemia rather than acute myelogenous leukemia. The BCR-ABL tyrosine kinase inhibitors have been successful in inducing hematologic remissions in patients in accelerated and blast crisis phase to CML. Prolonged remissions are uncommon. However, higher doses of BCR-ABL tyrosine kinase inhibitors combined with other drugs may improve outcomes.

Allogeneic stem cell transplantation may be used in this more advanced phase of the disease in younger patients. Stem cell transplantation is less successful in the accelerated phase or in blast crisis than in the chronic phase, but it can produce remissions in some patients. In addition, some patients may achieve a remission with a BCR-ABL tyrosine kinase inhibitor, providing the time to do allogeneic stem cell transplantation in a more favorable circumstance, with improved outcomes.

# Other Related Disorders

The term "chronic myelogenous leukemia" can also be used to categorize other myelogenous leukemias that have a chronic course.

Chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia and chronic neutrophilic leukemia are considered to be forms of CML. However, these diseases are not BCR-ABL-positive CML. They are subtypes of myelogenous leukemia that progress more slowly than acute myelogenous leukemia. In general, these less common subtypes of CML create more severe disturbances in blood cell counts early in the course of the disease, and these disturbances are not as well controlled with current drug treatments. The fact that patients with these disorders do not have the BCR-ABL gene mutation is one of several distinguishing features used to make a diagnosis. The Society's free fact sheet, *The Chronic Myelomonocytic Leukemias (CMML)* provides more information on these disorders.

Patients with BCR-ABL-negative CML who do not fit the diagnostic criteria for CMML are often given the designation of atypical CML because their disease cannot be adequately described by criteria representative of CMML or CML. A small number of cases of CML have a mutation that does not involve BCR or ABL, but patients with

disease attributable to this type of mutation respond to imatinib. Dasatinib is being studied in clinical trials to see if it is an effective treatment for CMML.

Chronic neutrophilic leukemia is a rare form of CML.

# Clinical Trials

New approaches to therapy are under study in clinical trials. These trials, conducted under rigorous guidelines, help physicians to determine the beneficial effects of new treatments and what, if any, adverse effects they have. New drugs, new types of immunotherapy and new approaches to stem cell transplantation are continually being explored to bring new and better treatments to the patient. The Society's Information Resource Center, (800) 955-4572, offers guidance on how patients can work with their physicians to find out if a specific clinical trial is an appropriate treatment option. Information specialists will conduct clinical trial searches for patients, family members and healthcare professionals. This service is also available online at the Society's Web site, www.LLS.org.

**New Targeted Agents for CML** Excellent results are associated with imatinib treatment for many patients. However, there is a need to improve CML therapy, especially for patients who do not tolerate or respond to imatinib and dasatinib, or who develop resistance to these drugs.

Another drug, nilotinib, has entered clinical trials and appears to be a useful alternative for patients with intolerance or resistance to imatinib. This drug is more potent than imatinib and can induce remission in a proportion of patients who have developed imatinib resistance.

Other questions to be explored in clinical trials for BCR-ABL tyrosine kinase inhibitors include:

- Would dasatinib be either just as effective or more effective than imatinib for initial treatment of chronic phase CML?
- Will nilotinib induce a response in patients who are resistant to imatinib or dasatinib?
- Would combinations of these drugs improve the frequency and length of patients' responses?

A compound called ON012380 has been found to be effective in all resistant CML cells in the test tube and in experimental animals, but it has not reached the point of human trials. One of the noteworthy features of this compound is that it attacks the ABL portion of BCR-ABL in a different site than imatinib and its newer counterparts, dasatinib and nilotinib. It also has inhibitory effects on mutations, such as T315I, that are resistant to these newer BCR-ABL tyrosine kinase inhibitors. If this chemical can be converted to a drug with acceptable toxicity, it should advance the treatment of CML significantly.

A phase I clinical trial is under way for VX-680, a drug called an "Aurora kinase inhibitor." VX-680 blocks the activity of various imatinib-resistant mutations, including T315I, which is resistant to dasatinib and nilotinib. One of the purposes of this trial is to evaluate the safety and tolerability of VX-680 in patients with CML in blast crisis. Aurora kinases are believed to play multiple roles in the development and progression of cancer, such as regulating cell growth, changing normal cells into cancer cells and decreasing the production of p53, one of the body's natural tumor suppressors.

**Vaccine Therapy** One goal of research for CML treatment is to develop a vaccine against the disease. This type of vaccine would not prevent the onset of the disease, as do vaccines for infectious diseases. Instead, the vaccine would heighten an immune attack against residual leukemia cells in an effort to keep the disease in remission for longer periods than would otherwise be the case.

CML has been shown to respond to immunotherapy, and thus this disease is a good candidate for study of a vaccine that supplements the effects of drug therapy. Three CML vaccines under study, AG-858, CMLVAX and PR1 are described in the Society's free publication, *Vaccine Therapy Facts*.

**Advances in Transplantation** Reduced-intensity chemotherapy followed by allogeneic stem cell transplantation (mini-transplants or nonmyeloablative transplants) is being studied to determine if this type of approach could be an effective treatment for CML. Instead of employing intensive chemotherapy to destroy the leukemic cells, the goal of this treatment is to permit the donor immune cells to engraft slowly and set up a graft versus leukemia effect that suppresses the leukemia.

Other drugs are being tested in clinical trials to enhance the graft versus leukemia effect of stem cell transplantation and to reduce the risks of high-grade graft versus host disease. In addition, research is under way using cord blood as a source of stem cells for transplantation in children and adults. This provides another potential source of matched, unrelated stem cells for those patients without 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.

Information on current clinical trials for these and other CML treatments can be obtained from the Society's Information Resource Center, (800) 955-4572 or through the Society's online Clinical Trial Service, at www.LLS.org.

# Social and Emotional Aspects

The diagnosis of CML may provoke a profound emotional response in the patient, family members and friends. Denial, depression, a feeling of hopelessness and fear are normal and usual reactions. No one response is either expected or unexpected.

"Why me?" is a common question patients ask. It is a normal reaction to a diagnosis of cancer and the need for treatment. Many emotions surface at the time of diagnosis and during treatment. The need for drug treatments and other therapies, and the realization that illness and treatment will cause some changes in one's life, can prompt a range of feelings.

People newly diagnosed with cancer face uncertainty about what comes next. Together, patients, families and healthcare providers can address concerns in a clear and straightforward manner. For many people, the beginning of treatment and the chance for remission bring emotional relief as the focus shifts to the treatment process ahead and the prospect of recovery.

**Children's Concerns** Children with cancer may feel frightened and helpless but may be too young to fully understand their illness or the treatment and its implications. Children with blood cancers may be dealing with absences from school, separation from friends and an inability to participate in certain activities, such as sports — at least for a time. Children who are ill may feel anger toward their healthcare team for "hurting" them, or toward their parents for allowing them to become ill or having to

undergo treatment. Reengaging the child in as many activities as possible is one of the best ways to soothe and reassure the child and minimize disruptions in the child's development.

Siblings of the child with cancer also may require special attention. They may fear the disease will strike them, feel guilt about their brother's or sister's illness and receive less time from parents who devote extra time to their ill child.

The parents of a child with cancer are often confused, angry and fearful. To complicate matters, disciplining a child with cancer, or the time commitment and financial burdens of the child's illness, may cause disagreements within the family. It is important for parents of a sick child to ask the healthcare team for help and guidance, not only for the child's medical concerns, but also for the child's emotional issues relating to the disease and its treatment. For more information, see the Society's booklet, *Emotional Aspects of Childhood Blood Cancers*.

**Treatment Choices** The process of making choices about drug therapy and other treatment options can cause a great deal of anxiety. Often, if people with blood cancers talk to their healthcare provider about the medical questions they have, they feel some sense of relief in making treatment choices. In addition, the patient's physicians, nurses, social workers and other healthcare professionals understand the complexity of emotions and special needs of those undergoing treatment. They are available to spend time with the patient, answer questions, lend emotional support and provide referrals to other useful resources.

**Family and Friends** The support of family and friends can contribute to a patient's ability to cope with what lies ahead. Many healthcare providers recommend that a friend or family member accompany a patient to treatments, especially for the first few times. The presence of a friend or family member may help ease anxiety. In addition, this person can act as an advocate, asking questions for the patient and listening to and retaining treatment information. Often, patients with cancer become acquainted with one another, and these friendships, too, can provide a support system.

**Lifestyle Changes** A change in lifestyle will occur for a patient with cancer and his or her family. Daily routines may have to be adjusted to accommodate treatment schedules. However, many individuals are able to carry out their day-to-day routines with few or no changes.

Stress and side effects associated with the diagnosis of cancer and its treatment will often cause a person to question his or her self-worth, identity and appearance. These feelings are common and may affect relationships, including sexual relationships. Sexual desire may decrease for a period of time, then return. Recognition that these feelings are normal, and that many side effects are temporary, may be reassuring. Open, honest communication regarding fears and concerns can be very helpful. The healthcare team will work toward minimizing any discomforts of treatment. Patients and families are encouraged to ask any questions or raise concerns related to emotional or social issues, so that the physician, nurses and social workers can help provide the answers and make referrals to available support groups, counseling services, or community programs. For more information, see the Society's free booklets, *Coping* and *Each New Day*.

The Leukemia & Lymphoma Society offers programs through its local chapters to help ease the emotional and economic pressures that come with a blood cancer diagnosis. Visit the Society's Web site at www.LLS.org or contact the Society's Information Resource Center at (800) 955-4572 to locate a chapter in your area, order free publications or speak directly to an Information Specialist.

# Glossary

**ABL**
The designation of the human proto-oncogene located on chromosome 9 that is mutated by the translocation of a piece of chromosome 9 to chromosome 22 in CML and some cases of acute lymphocytic leukemia. The mutation of this gene causes CML. The abbreviation for the gene derives from the name of the scientist, Dr. Harvey Abelson, who discovered the gene while studying cancer-causing viruses in mice.

**Allogeneic Stem Cell Transplantation**
The transfer of stem cells from one person (the donor) to another (the recipient). The closer the similarity between the donor and the recipient, the higher the probability that the transplant will be a success and harmful immune reactions will be minimized. Siblings of the same sex are the most likely to be closely matched, but other family members and unrelated matched donors can be similar enough to achieve a successful transplant if the optimal match is not available and the severity of illness justifies the risk. See the Society's free booklet *Blood and Marrow Stem Cell Transplantation* for more information.

**Anemia**
A decrease in the red cells and therefore the hemoglobin concentration of the blood. This results in a decreased capacity of the blood to carry oxygen. If severe, anemia can cause a pale complexion, weakness, fatigue and shortness of breath on exertion.

**Apheresis** (see Hemapheresis)

**Autologous Stem Cell Infusion**
A treatment that involves harvesting a patient's blood or marrow stem cells, which are often frozen for later use. The patient is then given intensive therapy and the stem cells are infused back into the patient via an indwelling catheter. The stem cells may be obtained from a patient in remission. The purpose of the treatment is to restore blood cell production from the stem cells that have been returned to the patient after intensive therapy has severely damaged the patient's marrow. This procedure uses peripheral blood stem cells with increasing frequency (see Hemapheresis). Autologous stem cell infusion differs from transplantation, a procedure involving taking tissue from one individual (donor) and giving it to another

(recipient). See the Society's free booklet *Blood and Marrow Stem Cell Transplantation* for more information.

**Autosome**
Term that refers to chromosomes 1 through 22. In addition to 22 pairs of autosomes, each cell contains two sex chromosomes, either XX (female) or XY (male).

**Banding of Chromosomes**
The staining of chromosomes with dyes that highlight transverse 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.

**Basophil**
A type of white cell that participates in certain allergic reactions.

**BCR-ABL Tyrosine Kinase Inhibitor** (see Tyrosine Kinase Inhibitor)

**Blast Cells**
The earliest marrow cells identified by the light microscope. Blasts represent about 1 percent of normally developing marrow cells. They are largely myeloblasts, which are cells that will develop into neutrophils. In normal lymph nodes, blasts are usually lymphoblasts; that is, cells that are part of lymphocyte development. In CML, examination of stained (dyed) blood cells with a light microscope shows a small proportion of leukemic blast cells and a larger proportion of maturing and fully matured white cells (myelocytes and neutrophils). In acute leukemias, blast cells accumulate in large numbers, comprising perhaps up to 80 percent of all marrow cells.

**Bone Marrow**
The bones are hollow and their central cavity is occupied by marrow, a spongy tissue that is the site of blood cell formation. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. Once marrow cells mature into blood cells, they enter the blood that passes through the marrow and are carried throughout the body. In the adult, the bones of the hands, feet, legs and arms are filled with fat cells rather than the marrow that generates blood cells.

**Bone Marrow Transplantation** (see Allogeneic Stem Cell Transplantation and Autologous Stem Cell Infusion)

**Chemotherapy**
The use of chemicals (drugs or medications) to kill malignant cells. Numerous chemicals have been developed for this purpose, and most act to injure the DNA of the cells. When the DNA is injured, the cells cannot grow or survive. Successful chemotherapy depends on the fact that malignant cells are somewhat more sensitive to the chemicals than normal cells. Because the cells of the marrow, the gastrointestinal tract, the skin and the hair follicles are most sensitive to these chemicals, injury to these organs causes the common side effects of chemotherapy; that is, mouth sores and hair loss.

**Chromosome**
All normal human cells with a nucleus contain 46 structures called chromosomes. The genes, specific stretches of DNA, are the principal structures that make up the chromosomes. An "average"-sized chromosome contains enough DNA to account for about 2,000 genes. The X and Y chromosomes are the determinants of our gender and are referred to as the sex chromosomes: two X chromosomes in females and an X and a Y chromosome in males. The number or shape of chromosomes may be altered in lymphoma or leukemia cells.

**Colony Stimulating Factor** (see Cytokines)

**Computed Tomography (CT) Scan**
A technique for imaging body tissues and organs. X-ray transmissions are converted to detailed images using a computer to synthesize x-ray data. The images are displayed as a cross-section of the body at any level from the head to the feet. A CT scan of the chest or abdomen permits detection of an enlarged lymph node, liver or spleen. A CT scan can be used to measure the size of these and other structures before, during and after treatment.

**Cord Blood Stem Cells**
Stem cells that are present in blood drained from the placenta and umbilical cord. 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 used by matched or nearly matched unrelated donors. Rarely, the transplant is between siblings.

**Cytogenetics**
The process of analyzing the number and shape of the chromosomes of cells. The individual who prepares, examines and interprets the number and shape of chromosomes in cells is called a cytogeneticist. In addition to identifying chromosome alterations, the specific genes affected can be identified in some cases. These findings are very helpful in diagnosing specific types of leukemia, in determining treatment approaches and in measuring response to treatment.

**Cytokines**
These are cell-derived chemicals that are secreted by various types of cells and act on other cells to stimulate or inhibit their function. Chemicals derived from lymphocytes are called "lymphokines." Chemicals derived from lymphocytes that act on other white cells are called "interleukins;" that is, they interact between two types of leukocytes. Some cytokines can be made commercially and used in treatment. Granulocyte-colony-stimulating factor (G-CSF) is one such cytokine. It stimulates the production of neutrophils and shortens the period of low neutrophil counts in the blood after chemotherapy. Cytokines that stimulate cell growth are sometimes referred to as "growth factors."

**Differentiation**
The process by which stem cells transform from cells without specific structural or functional characteristics into functional cells of a single blood cell line. The process of differentiation of stem cells forms the red cells, platelets, neutrophils, monocytes, eosinophils, basophils and lymphocytes.

**Eosinophil**
A type of white cell that participates in allergic reactions and helps to fight certain parasitic infections.

**Erythrocytes** (see Red Cells)

**Fluorescence In Situ Hybridization**
A laboratory test, referred to as FISH, which is a means to detect chromosome abnormalities. "In situ" refers to something that occurs in its natural or original position. FISH studies examine genes on chromosomes in their natural position. This approach can be used on blood as well as marrow cells and does not require that the cell be in a specific phase of cell division for its use, as is the case in classical tests for chromosome abnormalities. In addition, the ability to examine blood cells obtained by routine procedures simplifies the process for the patient.

### Graft Versus Host Disease

The immune attack by lymphocytes in a donor's marrow or blood cell suspension (the graft) against the tissues of a recipient (the host). The immune cells most engaged in this reaction are donor T lymphocytes, which are present in the donor's blood or marrow, the source of stem cells. The principal organs injured are the skin, the liver and the gastrointestinal tract. The reaction does not occur in transplantation between identical twins. The reaction may be minimal in closely matched individuals or severe in less well-matched individuals. The reaction is mediated in part by antigens that are not in the human leukocyte antigen(s) HLA system and cannot be matched prior to transplant. These are referred to as "minor histocompatability antigens." For example, in the case of a female stem cell donor and a male recipient, the female donor's cells that do not share the genes on the Y chromosome may interpret factors that are produced by genes on the Y chromosome as foreign. This fact does not prohibit female donors for male recipients, but it makes the risk of immune reaction higher.

### Graft Versus Leukemia Effect

Transplanted T lymphocytes may not only attack the recipient's normal tissues (graft versus host) but may recognize and attack the malignant cells in the recipient. This effect was noted when 1) leukemia recurrence after transplantation was seen to be more likely if the donor and recipient were identical twins than if they were not, 2) the more prominent the graft versus host disease, the less likely was leukemia recurrence, and 3) the removal of donor T lymphocytes decreased graft versus host disease but also resulted in a higher frequency of leukemia relapse. Each of these observations could best be explained by an immune attack by donor lymphocytes against recipient leukemia cells. This effect seems to be most active in CML, although it may occur in patients with myeloma and other blood cancers as well.

### Granulocyte

A type of white cell that has a large number of granules in the cell body. Neutrophils, eosinophils and basophils are types of granulocytes.

### Granulocytic Sarcoma

A local tumor composed of leukemic myeloblasts and sometimes related myeloid cells. These tumors are outside the marrow and may occur beneath the skin or in many other sites. They may be the first evidence of leukemia or may occur after the disease has been diagnosed.

**Granulocytosis**
An increase above normal of the concentration of blood leukocytes (white cells) that fall into the category of granulocytes (neutrophils, eosinophils and basophils). This designation excludes lymphocytes and monocytes.

**Growth Factors** (see Cytokines)

**Hemapheresis**
The process of removing a donor's blood to extract a specific component and returning the remaining parts to the donor. The process uses continuous circulation of blood from a donor through an apparatus and back to the donor. This process makes it possible to remove desired elements from large volumes of blood. Platelets, red blood cells, white cells, or plasma can be removed, separately. For example, this technique permits the harvest of enough platelets for a platelet transfusion from one donor (rather than six to eight separate donors). In so doing, the recipient of the platelets is exposed to the blood of fewer donors or can be given HLA-matched platelets from a single related donor. This technique is also used to remove circulating blood stem cells that can be frozen, stored, and, later, used instead of marrow stem cells for transplantation. The system of hemapheresis is closed and sterile.

**Hematologist**
A physician who specializes in the treatment of blood cell diseases. This person is either an internist who treats adults or a pediatrician who treats children. Hematopathologists are pathologists who specialize in the diagnosis of blood cell diseases and who perform the specialized laboratory tests often required to make a conclusive diagnosis.

**Hematopoiesis**
The process of blood cell development in the marrow. The most undeveloped cells in the marrow are stem cells. They start the process of blood cell development. The stem cells begin to develop into young or immature blood cells like red cells or white cells of various types. This process is called "differentiation." The young or immature blood cells further develop into fully functional blood cells. This process is called "maturation." The cells then leave the marrow and enter the blood and circulate throughout the body. Hematopoiesis is a continuous process that is normally active throughout life. Most blood cells live for short periods and must be continuously replaced. Red cells die in four months, platelets in 10 days and most

neutrophils in two or three days. About 500 billion blood cells are made each day. This requirement for very rapid replacement explains the severe deficiency in blood cell counts when the marrow is injured by replacement with leukemia, lymphoma or myeloma cells.

### HLA

The acronym for human leukocyte antigens. These proteins are on the surface of most tissue cells and give an individual his or her unique tissue type. HLA factors are inherited from mother and father, and the greatest chance of having the same HLA type is between siblings. On average, one in four siblings is expected to share the same HLA type. The testing for HLA antigens is referred to as "tissue typing." There are six major groups of HLA antigens: A, B, C, D, Dr and Dq. These proteins on the surface of cells act as antigens when donated (transplanted) to another individual, the recipient. If the antigens on the donor cells are identical (e.g., identical twins) or very similar (e.g., HLA-matched sibling), the transplant (donated stem cells) is more likely to survive (engraft) in the recipient. In addition, the recipient's body cells are less likely to be attacked by the donated immune cells (graft versus host disease).

### Hyperleukocytosis

The term applies to patients with leukemia who at the time of diagnosis have an extremely elevated white cell count. This circumstance occurs most frequently in patients with CML. If the condition is severe enough, blood flow may be impaired by the very high concentration of leukocytes. Urgent treatment with hemapheresis and chemotherapy is usually administered if symptoms are severe.

### Immunophenotyping

A method that uses the reaction of antibodies with cell antigens to determine a specific type of cell in a sample of blood cells, marrow cells or lymph node cells. The antibodies react with specific antigens on the cell. A tag is attached to the antibody so that it can be detected. The tag can be identified by the laboratory equipment used for the test. As cells carrying their array of antigens are tagged with specific antibodies, they can be identified; for example, myelogenous leukemic cells can be distinguished from lymphocytic leukemic cells. Normal lymphocytes may be distinguished from leukemic lymphocytes. This method also helps to subclassify cell types, which may, in turn, help the physician to decide on the best treatment to apply in that type of leukemia or lymphoma. The antigen on a cell is referred to as "cluster of differentiation" or "CD," with an associated number. For example, CD16 may be present on leukemic lymphoblasts and CD33 on leukemic myeloblasts.

**Indwelling Catheter**
Several types of catheters (e.g., Hickman®, Broviac®, others) can be used for patients receiving intensive chemotherapy or nutritional support. An indwelling catheter is a special tubing inserted into a large vein in the upper chest. The catheter is tunneled under the skin of the chest to keep it firmly in place. The external end of the catheter can be used to administer medications, nutritional fluids or blood products or to withdraw blood samples. With meticulous care, catheters can remain in place for long periods of time (many months), if necessary. They can be capped and remain in place in patients after they leave the hospital and used for outpatient chemotherapy or blood product administration.

**Interleukin** (see Cytokines)

**Karyotype**
The systematic arrangement, using images, of the 46 human chromosomes of a cell in 22 matched pairs (maternal and paternal member of each pair) by length from longest to shortest and other features. These 22 pairs are referred to as "autosomes." The sex chromosomes are shown as a separate pair (either XX or XY).

**Leukocyte Alkaline Phosphate (LAP)**
A neutrophil enzyme that is markedly decreased in its activity in patients with CML. It was formerly used to distinguish the increase in white cell count in CML from other causes of increased white cell count. The test has been replaced by measurement of BCR gene rearrangement, a more specific alteration present in virtually all patients with CML.

**Leukocytes**
A synonym for white cells (see White Cells).

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

**Leukopenia**
A decrease below normal levels in the concentration of blood leukocytes (white cells).

**Lymph Nodes**
Small structures, the size of beans, that contain large numbers of lymphocytes and are connected with each other by small channels called lymphatics. These nodes are distributed throughout the body. Enlarged lymph nodes can be seen, felt or measured by computed tomography (CT) scan or magnetic resonance imaging (MRI) depending on the degree of enlargement and location.

**Lymphocyte**
A type of white cell that is an essential part of the body's immune system. There are three major types of lymphocytes: B lymphocytes, which produce antibodies to help combat infectious agents like bacteria, viruses and fungi; T lymphocytes, which have several functions, including assisting B lymphocytes to make antibodies; and natural killer (NK) cells that can attack virus-infected cells or tumor cells.

**Lymphokine** (see Cytokines)

**Magnetic Resonance Imaging (MRI)**
A technique that provides detailed images of body structures. It differs from a CT scan in that the patient is not exposed to x-rays. The signals generated in the tissues in response to a magnetic field produced by the instrument are converted by computer into images of body structures. Thus, the size and a change in size of tumor masses or organs, such as the lymph nodes, liver and spleen, can be measured.

**Molecular-Targeted Therapy**
The use of drugs that have been designed to target specific abnormalities thought to be causing cell disturbances that result in disease. (See Tyrosine Kinase Inhibitors.)

**Monocyte (Macrophage)**
A type of white cell that represents about 5 to 10 percent of the cells in normal human blood. The monocyte, along with the neutrophil, are the two major microbes in the blood that destroy cells. When monocytes leave the blood and enter the tissue, they are converted to macrophages. The macrophage is the monocyte in action; it can combat infection in the tissues, ingest dead cells and assist lymphocytes in their immune functions.

## Multidrug Resistance

A characteristic of cells that makes them resistant to the effects of several different classes of drugs. There are several forms of drug resistance, each determined by genes that govern how the cell will respond to the chemical agents. One type of multidrug resistance (or MDR) involves the ability to eject several drugs out of cells. The cell outer wall or membrane of the cell contains a pump that ejects chemicals, preventing them from reaching a toxic concentration. The resistance to drugs can be traced to the expression of genes that direct the formation of high amounts of the protein that prevents the drugs from having their effects on the malignant cells. If the gene or genes involved are not expressed or are weakly expressed, the cells are more sensitive to the drug's effect. If the genes are highly expressed, the cells are less sensitive to the drug's effect.

## Mutation

An alteration in a gene that results from a change to the sequence of the DNA that represents a specific gene. A "germ cell mutation" is present in the egg or the sperm and can be transmitted from parent(s) to offspring. A "somatic cell mutation" occurs in a specific tissue cell and can result in the growth of the specific tissue cell into a tumor. Most cancers start after a somatic cell mutation. In CML a primitive marrow cell undergoes a somatic mutation(s) that leads to the formation of leukemic cells.

## Neutropenia

A decrease below normal in the concentration of neutrophils, a type of white cell.

## Neutrophils

The principal phagocyte (microbe-eating) cell in the blood. This blood cell is the main cell that combats infections. Often, it is not present in sufficient quantities in patients with acute leukemia or after chemotherapy. A severe deficiency of neutrophils increases the patient's susceptibility to infection. A neutrophil may be called a "poly" (polymorphonuclear neutrophil) or "seg" (segmented neutrophil) because its nucleus has several lobes.

## Oncogene

A mutated gene that is the cause of a cancer. Nearly all cases of CML have a consistent mutated gene (oncogene); certain subtypes of acute myelogenous leukemia, acute lymphocytic leukemia and lymphoma are also associated with specific oncogenes.

### Oncologist
A physician who diagnoses and treats patients with cancer. Oncologists are usually internists who treat adults or pediatricians who treat children. Radiation oncologists specialize in the use of radiation to treat cancer, and surgical oncologists specialize in the use of surgical procedures to diagnose and treat cancer. These physicians cooperate and collaborate to provide the best treatment plan (surgery, radiation therapy or chemotherapy) for the patient.

### Pancytopenia
A decrease below normal in the concentration of the three major blood cell types: red cells, white cells and platelets.

### Petechiae
Pinhead-sized sites of bleeding in the skin. This type of bleeding results from a very low platelet count. The small punctate hemorrhages are frequently seen on the legs, feet, trunk and arms. They evolve from red to brown and eventually disappear. They stop developing when the platelet count increases.

### Phagocytes
Cells that readily eat (ingest) microorganisms like bacteria or fungi and can kill them as a means of protecting the body against infection. The two principal phagocytes are neutrophils and monocytes. They emigrate from the blood and into tissues in which an infection has developed. A severe decrease in the number of these cells in the blood is the principal cause of susceptibility to infection in patients treated with intensive radiotherapy and/or chemotherapy. The ltreatment suppresses blood cell production in the marrow, resulting in deficiencies of these phagocytic cells.

### Philadelphia Chromosome or Ph Chromosome
The name applied to the abnormality of the chromosome number 22 in the marrow and blood cells of patients with chronic myelogenous leukemia. The abnormality reflects a shortened long arm of chromosome number 22. The observation was reported first by physicians at the University of Pennsylvania and named the Philadelphia chromosome. Since its discovery, the piece of chromosome lost has been shown to stick (translocate) to chromosome 9 in most cases. Indeed, some of chromosome 9 sticks (translocates) to chromosome 22. This 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 chromosome, the addition to chromosome 9 was less apparent than the shortening of 22 until more sensitive techniques became available. The abnormality of chromosome 22 is now usually referred to in its abbreviated form as the Ph chromosome.

### Platelets

Small blood cells (about one-tenth the volume of red cells) that stick to the site of blood vessel injury, clump together and seal off the injured blood vessel to stop bleeding. "Thrombocyte" is a synonym for platelet and is often used as the prefix in terms describing disorders of platelets, such as thrombocytopenia or thrombocythemia.

### Platelet Transfusion

The transfusion of donor platelets is frequently needed to support patients treated for acute leukemia. The platelets can be pooled from several unrelated donors and given as pooled random-donor platelets. It requires the platelets from about six one-unit blood donors to significantly raise the platelet count in a recipient. Sufficient platelets can be obtained from one donor by apheresis. This technique involves skimming the platelets from large volumes of blood passing through the apheresis machine. The red cells and plasma are returned to the donor. Patients receiving single-donor platelets are not exposed to the different antigens on platelets from many different people, and they are less likely to develop antibodies against donor platelets. HLA-matched platelet transfusion can be given from a related donor with an identical or very similar HLA tissue type. The platelets are collected by 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 leukemia or lymphoma cells, too few to be seen even with a microscope. The technique can detect the presence of one leukemic cell among 500,000 to one million nonleukemic cells. PCR requires a specific DNA (or RNA) abnormality or marker, like an oncogene, in the leukemic or lymphomatous cells in order to identify residual abnormal cells.

### Red Cells

Blood cells that contain hemoglobin. Hemoglobin binds oxygen when red cells pass through the lung and releases it to the tissues of the body. The red cells make up a little less than half the volume of blood in healthy individuals.

**Relapse or Recurrence**
A return of the disease after it has been in remission following treatment.

**Remission**
A disappearance of evidence of a disease, usually as a result of treatment. The terms "complete" or "partial" are used to modify the term "remission." Complete remission means all evidence of the disease is gone. Partial remission means the disease is markedly improved by treatment, but residual evidence of the disease is present. Long-term benefit usually requires a complete remission, especially in acute leukemia or progressive lymphomas.

**Resistance to Treatment**
The ability of cells to live and divide despite their exposure to a chemical that ordinarily kills cells or inhibits their growth. This is the cause of refractory leukemia, whereby a proportion of leukemic cells resists the damaging effects of a drug or drugs. Cells have several ways to develop drug resistance (see Multidrug Resistance).

**Somatic Mutation** (see Mutation)

**Spleen**
An organ of the body in the left upper portion of the abdomen just under the left side of the diaphragm. It contains clusters of lymphocytes and also filters the blood of old or worn-out cells. It is often affected in lymphocytic leukemias and lymphomas. Enlargement of the spleen is referred to as "splenomegaly." Removal of the spleen by surgery is referred to as "splenectomy." Removal of the spleen is used to treat certain diseases. Most of the functions of the spleen can be performed by other organs, such as the lymph nodes and liver.

**Stem Cells**
These are primitive cells in marrow that are required to make red cells, white cells and platelets. Generally, the stem cells are largely found in the marrow, but some leave the marrow and circulate in the blood. Using special techniques, the stem cells in blood can be collected, preserved by freezing and, later, thawed and used for stem cell therapy. (See Hematopoiesis.)

## Stem Cell Transplantation

This treatment was developed to restore the marrow of patients who had lethal injury to that site. Such injury can occur because of primary marrow failure, destruction of marrow by disease or intensive chemical or radiation exposure. As first designed, the source of the transplant was the marrow cells of a healthy donor who had the same tissue (HLA) type as the patient. Usually, the source was a brother or sister. Donor programs have been established to identify unrelated donors who have a matching tissue type. This approach requires screening tens of thousands of unrelated individuals of similar ethnicity. The transplant product is a very small fraction of the marrow cells, called "stem cells." These stem cells not only reside in the marrow but also circulate in the blood. They can be harvested from the blood of a donor by treating the donor with an agent or agents that cause a release of larger numbers of stem cells into the blood and collecting them by hemapheresis. The stem cells circulate in large numbers in fetal blood also, and can be recovered from the placental and umbilical cord blood after childbirth. The harvesting, freezing and storing of "cord blood" has provided another source of stem cells for transplantation. Since blood as well as marrow is a very good source of cells for transplantation, the term "stem cell transplantation" has replaced "bone marrow transplantation" as the general term for these procedures. If the donor is an identical twin, the transplant is called "syngeneic," the medical term for genetically identical. If the donor is a nonidentical sibling, the transplant is called "allogeneic," indicating it is from the same species and in practice nearly always matching in tissue type. The term "matched-unrelated" is applied to the donor recruited from large-volume screening programs searching for the rare individual who is very similar in tissue type to the patient. (See also Allogeneic Stem Cell Transplantation and Autologous Stem Cell Infusion.)

## Thrombocytopenia

A decrease below normal in the concentration of the blood platelets.

## Translocation

An abnormality of chromosomes in marrow or lymph node cells, which occurs when a piece of one chromosome breaks off and sticks to the end of another chromosome. In a balanced translocation, each of two chromosomes has a piece broken off, and the lost piece sticks to the broken end of the other chromosome. The gene at which the break occurs is altered. This is one form of a somatic mutation that may transform the gene into an oncogene, or cancer-causing gene.

### Tumor Suppressor Gene (Anti-Oncogene)

A gene that acts to prevent cell growth. If a mutation occurs in this gene, it may make the individual more susceptible to the development of cancer in the tissue in which the mutation occurs. This effect is a recessive effect in that each of the pair of genes normally present must be abnormal for the tumor-promoting action to occur.

### 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 number 9, directs its production. In CML, the DNA alteration 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

A type of drug, the most noteworthy of which is imatinib mesylate, which blocks 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.

### White Cells

A synonym for leukocytes. There are five major types of white cells in the blood: neutrophils, eosinophils, basophils, monocytes and lymphocytes.

# Resources

## The Leukemia & Lymphoma Society Patient Publications

*Blood and Marrow Stem Cell Transplantation.* The Leukemia & Lymphoma Society. 2005.

*Coping – Support for People Living with Leukemia, Lymphoma or Myeloma*. The Leukemia & Lymphoma Society. 2005.

*Cord Blood Stem Cell Transplantation.* The Leukemia & Lymphoma Society. 2005.

*Each New Day.* The Leukemia & Lymphoma Society. 2006.

*The Chronic Myelomonocytic Leukemias (CMML)*. The Leukemia & Lymphoma Society. 2002.

*Understanding Drug Therapy and Managing Side Effects.* The Leukemia & Lymphoma Society. 2006 (in press).

*Vaccine Therapy Facts.* The Leukemia & Lymphoma Society. 2006.

## Technical Sources

Kantarjian HM, Cortes J. New strategies in chronic myeloid leukemia [review]. *Int J Hematol.* 2006;83:289-293.

Lichtman MA, Beutler E, Kipps TJ, et al, eds. Principles of hematopoietic cell transplantation; chronic myelogenous leukemia and related disorders. In: *Williams Hematology*. 7th ed. McGraw-Hill Book Company; 2006: chap 22, chap 88.

Quintas-Cardama A, Cortes JE. Chronic myeloid leukemia: diagnosis and treatment (review). *Mayo Clin Proc*. 2006;81:973-988.

Savona M, Talpaz M. Chronic myeloid leukemia: changing the treatment paradigms. *Oncology* (*Williston Park*). 2006;20:707-711; discussion 712-714, 719, 724.

## Nontechnical Sources

The Society's Discussion Board is an online source of support and information for patients and families living with CML. It can be accessed through the Society's Web site. Questions and comments can be posted. The Discussion Board is divided into subforums specific to various aspects of living with blood cancers. "Living with CML" is one of the forums. It can be accessed at: www.leukemia-lymphoma.org. Click on "Discussion Boards," then click on "Living with CML."


Buchholz WM, Buchholz SW. *Live Longer*, *Live Larger: A Holistic Approach for Cancer Patients and Their Families.* O'Reilly & Associates, Inc; 2001.

Groopman J, *Second Opinions: Stories of Intuition and Choice in the Changing World of Medicine.* New York, NY: Penguin USA; 2001.

Harpham WS. *Diagnosis Cancer: Your Guide to the First Few Months of Healthy Survivorship, Expanded and Updated*. New York, NY: WW Norton; 2003.

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Holland JC, Lewis S. *The Human Side of Cancer: Living with Hope, Coping with Uncertainty*. New York, NY. HarperCollins; 2000.

Lynn J, Harrold J. *Handbook for Mortals: Guidance for People Facing Serious Illness.* New York, NY: Oxford University Press; 2001.

Oster N, Thomas L, Joseff D. *Making Informed Medical Decisions: Where to Look and How to Use What You Find.* O'Reilly & Associates, Inc; 2000.

# Notes

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Call Our Information Resource Center
The Society's Information Resource Center (IRC) provides patients, families and healthcare professionals with the latest information on leukemia, lymphoma and myeloma. Our information specialists – master's level oncology professionals – are available by phone (800.955.4572) Monday through Friday, 9 am to 6 pm (ET); via email (infocenter@LLS.org); or chat online at www.LLS.org (click on "Live Help").
Call 800.955.4572 for a complete directory of our patient services programs.
The Leukemia & Lymphoma Society
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For more information, please contact:

or:

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