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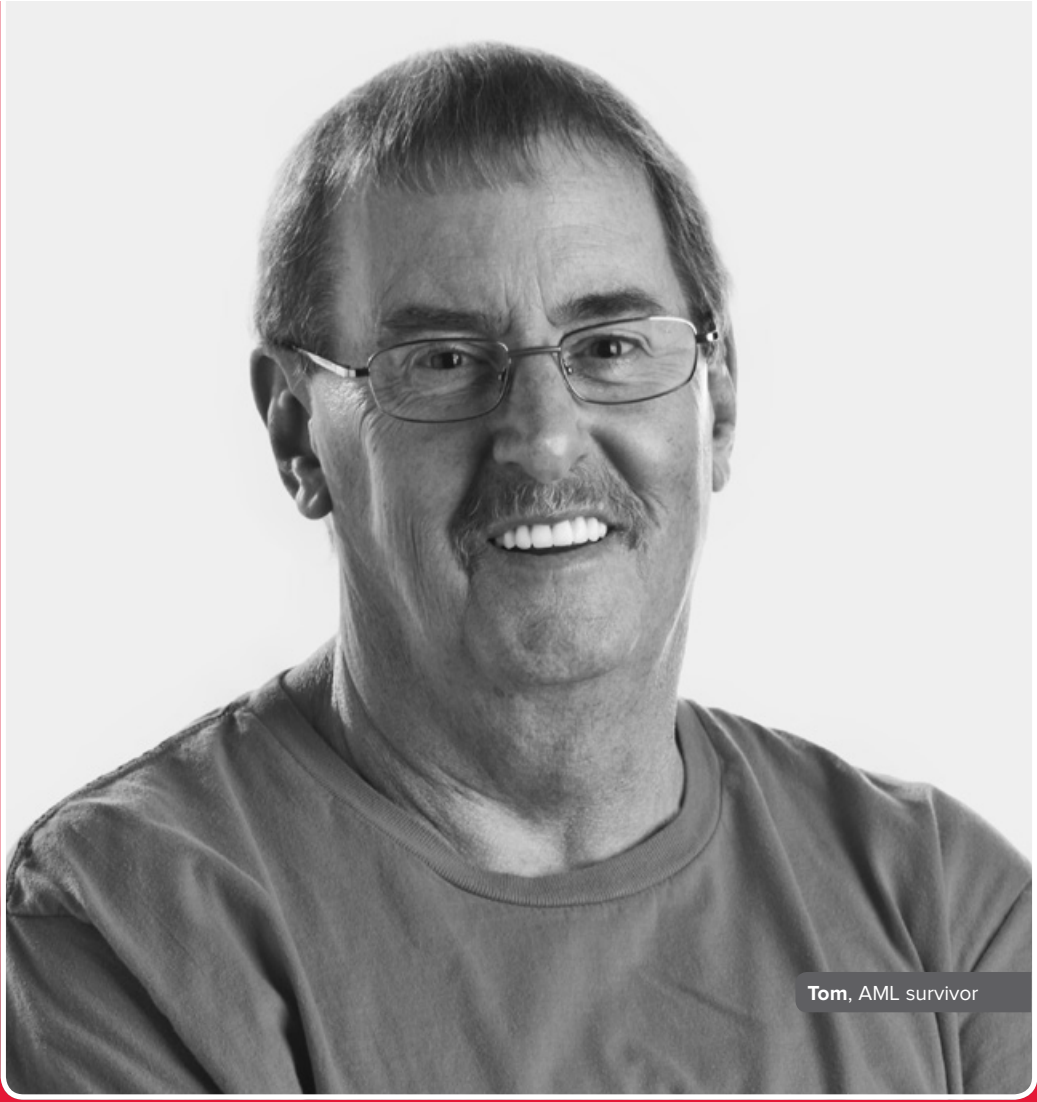
LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Acute Myeloid **Leukemia**



Tom, AML survivor

Revised **2011**

A Message from Louis J. DeGennaro, PhD

President and CEO of The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society (LLS) is committed to bringing you the most up-to-date blood cancer information. We know how important it is for you to have an accurate understanding of your diagnosis, treatment and support options. With this knowledge, you can work with members of your oncology team to move forward with the hope of remission and recovery. Our vision is that one day the great majority of people who have been diagnosed with Acute Myeloid Leukemia (AML) will be cured or will be able to manage their disease with a good quality of life. We hope that the information in this booklet will help you along your journey.

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. Since the first funding in 1954, LLS has invested more than $814 million in research specifically targeting blood cancers. We will continue to invest in research for cures and in programs and services that improve the quality of life of people who have AML and their families.

We wish you well.

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

This booklet provides information about acute myeloid leukemia (AML) for patients and their families. Brief descriptions of normal blood and marrow and definitions of medical terms are included at the end of the booklet to help readers better understand the information about AML.

AML may be called by other names, including acute myelogenous leukemia, acute myelocytic leukemia, acute myeloblastic leukemia and acute granulocytic leukemia.

About 12,950 new cases of AML were expected to be diagnosed in the United States in 2011. As of January 2008 an estimated 30,993 people were living with (or were in remission from) AML. Although AML can occur at any age, adults aged 60 years and older are more likely to develop the disease than younger people.[1]

Advances in AML testing and treatment are resulting in improved remission and cure rates, but much work remains to be done. For example, the vitamin A derivative all-*trans* retinoic acid (ATRA) has greatly improved survival rates for patients with acute promyelocytic leukemia (APL), a subtype of AML. A number of new therapies are under study in clinical trials.

[1]Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, www.seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER website, 2011.

Here to Help

This booklet will help you talk to your doctor about the tests and treatment you need. We encourage you to take the lead in asking questions and discussing your fears and concerns. These actions will give members of your healthcare team the opportunity to answer your questions, extend emotional support and provide any needed referrals.

A diagnosis of AML is often a shock to the patient, family members and friends. Denial, depression, hopelessness and fear are some of the reactions people may have. Keep in mind that

- Many people are better able to cope once they begin treatment and can look forward to recovery.
- The outlook for people with AML is continuing to improve. New approaches to therapy are being studied in clinical trials for patients of all ages and at every stage of treatment.

LLS Has Ways to Help. Treatment for AML will affect your daily life, at least for a time. You may have questions about your treatment and want to have friends, family members or caregivers help you get information.

Making treatment choices, paying for medical care, communicating with healthcare providers, family members and friends—these are some of the stressors that go along with a cancer diagnosis. LLS offers free information and patient services for individuals and families touched by blood cancers.

Speak to an Information Specialist. Information Specialists are master's level oncology professionals. They provide accurate up-to-date disease and treatment information and are available to speak with callers Monday through Friday, 9 a.m. to 6 p.m. ET at (800) 955-4572. You can email infocenter@LLS.org or chat live with a Specialist at www.LLS.org.

Language Services. Free language services are available when you speak with an Information Specialist. Let your doctor know if you want a professional healthcare interpreter who speaks your native language or uses sign language to be present during your visit. Many times, this is a free service.

Información en Español. LLS has a number of resources available in Spanish for patients, caregivers and healthcare professionals. You can read and download these resources online at www.LLS.org/espanol or order printed copies by mail or phone.

Other Helpful Organizations. Our website, www.LLS.org/resourcedirectory, offers an extensive list of resources for patients and families about financial assistance, counseling, transportation, summer camps and other needs.

Chapter Programs and Services. LLS chapter offices around the United States and Canada offer support and education. Your chapter can arrange for peer-to-peer support through the *Patti Robinson Kaufmann First Connection Program*. The *Patient Financial Aid* program offers a limited amount of financial aid for qualified patients. Find your local chapter by calling (800) 955-4572 or by visiting www.LLS.org/chapterfind.

Clinical Trials. Our Information Specialists help patients work with their doctors to find out about specific clinical trials. Information Specialists conduct clinical-trial searches for patients, family members and healthcare professionals. You can also use TrialCheck®, an online clinical-trial search service supported by LLS that offers patients and caregivers immediate access to listings of blood cancer clinical trials. Please visit www.LLS.org/clinicaltrials.

Free Materials. LLS publishes many free education and support materials for patients and healthcare professionals. PDF files can be read online or downloaded. Free print versions can be ordered. Visit www.LLS.org/resourcecenter.

Telephone/Web Education Programs. LLS provides a number of free, live telephone and web education programs presented by experts for patients, caregivers and healthcare professionals. For more information, visit www.LLS.org/programs.

Suggestions From Other People Living With Cancer

- Get information about choosing a cancer specialist or treatment center.
- Find out about financial matters: What does your insurance cover? What financial assistance is available to you?
- Learn about the most current tests and treatments for your type of AML.
- Keep all appointments with the doctor and talk openly about your fears or concerns or any side effects you experience.
- Talk with family and friends about how you feel and how they can help.
- Contact your doctor if you have fatigue, fever, pain or sleep problems so that any issues can be addressed early on.
- Get medical advice if you have experienced changes in mood, feelings of sadness or depression.

The Trish Greene Back to School Program for Children With Cancer. This program is designed to increase communication among parents, children, adolescents, young adults, healthcare professionals and school personnel. Informative materials, videos and a wealth of literature are available through LLS chapters to help ensure a smooth transition back to school. For more information, please visit www.LLS.org/backtoschool. For practical guidance on how to support your child, yourself and other family members, see the free LLS booklet *Coping With Childhood Leukemia and Lymphoma*.

Reach Out. You and your loved ones can reach out for support in several ways. For example:

- LLS offers online Blood Cancer Discussion Boards as well as online chats at www.LLS.org/getinfo.
- Local or Internet support groups and blogs can provide forums for support.
- Patients with cancer often become acquainted with one another, and these friendships provide support.

Depression. Treatment for depression has proven benefits for people living with cancer. Depression is an illness that should be treated even when a person is undergoing AML treatment. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a 2-week period. Contact LLS or ask your healthcare team for guidance and referrals to other sources of help, such as counseling services or community programs. For more information you can contact the National Institute of Mental Health (NIMH) at www.nimh.nih.gov and enter "depression" in the search box at the top of the web page, or call the NIMH toll-free at (866) 615-6464.

We'd Like to Hear From You. We hope this booklet helps you. Please tell us what you think at 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 and chronic lymphocytic leukemia.

Acute leukemias are rapidly progressing diseases that affect cells that are not fully developed. These cells cannot carry out their normal functions. Chronic leukemias usually progress more 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 31).

With myeloid leukemia, a cancerous change begins in a marrow cell that normally forms certain blood cells—that is, red cells, some types of white cells and platelets. With lymphocytic (lymphoblastic) leukemia, the cancerous change begins in a marrow cell that normally forms lymphocytes (another type of white cell).

The four main types of leukemia are further classified into subtypes. Knowing the subtype of your disease is important because the treatment approach may be based on the subtype (see *AML Subtypes* on page 11).

More general information about leukemia is given in the free LLS publication *Understanding Leukemia*.

Acute Myeloid Leukemia

How AML Develops. AML results from acquired changes in the DNA (genetic material) of a developing marrow cell. Once the marrow cell becomes a leukemic cell, it multiplies into 11 billion or more cells. These cells, called "leukemic blasts," do not function normally. However, they grow and survive better than normal cells.

The presence of the leukemic blasts blocks the production of normal cells. As a result, when AML is diagnosed, the number of healthy blood cells (red cells, white cells and platelets) is usually lower than normal.

The medical term for	Is
Low red cell count	Anemia
Low platelet count	Thrombocytopenia ("thrombocyte" is another word for platelet)
Low neutrophil count	Neutropenia (a neutrophil is a type of white cell)

Causes and Risk Factors. Most patients diagnosed with AML have no clear-cut triggering event.

Repeated exposure to the chemical benzene can be a factor in AML development. Benzene damages the DNA of normal marrow cells. According to the Agency for Toxic Substances and Disease Registry, despite the fact that petroleum products contribute to the majority of benzene in the atmosphere, half of the total national personal exposure to benzene comes from cigarette smoke. Benzene is also found in certain industrial settings; however, the strict regulation of its use has decreased benzene exposure in the workplace.

A small but increasing percentage of AML cases arise following treatment with chemotherapy (especially with alkylating agents or topoisomerase II inhibitors) or radiation therapy for other cancers, such as lymphoma, myeloma and breast cancer. But only a small proportion of people exposed to chemotherapy, radiation therapy and/or benzene develop AML. A theory about why AML develops in some people is that they have inherited genes that limit their ability to detoxify the causative agents.

Genetic disorders, such as Fanconi's anemia, Shwachman syndrome, Diamond-Blackfan syndrome and Down syndrome, are associated with an increased risk of AML. Very rarely, an unexpectedly high number of cases of AML may be diagnosed within the same family. Clusters of AML in unrelated people within a community are uncommon. AML is not contagious.

AML may develop from the progression of other blood cancers, including polycythemia vera, primary myelofibrosis, essential thrombocythemia and myelodysplastic syndromes (MDS).

Incidence. AML is the most common acute leukemia affecting adults. Older people are more likely to develop AML than younger adults or children. However, AML is the most common type of leukemia diagnosed during infancy. About 15 to 20 percent of cases of acute childhood leukemia and 80 percent of cases of acute adult leukemia are AML.

The risk for developing AML increases about 10-fold from ages 30 to 34 years (about 1 case per 100,000 people) to ages 65 to 69 years (about 10 cases per 100,000 people). For people over 70, the incidence rate continues to increase, peaking between the ages of 80 and 84 (see Figure 1).

Acute Myeloid Leukemia: Age-Specific Incidence Rates (2004-2008)

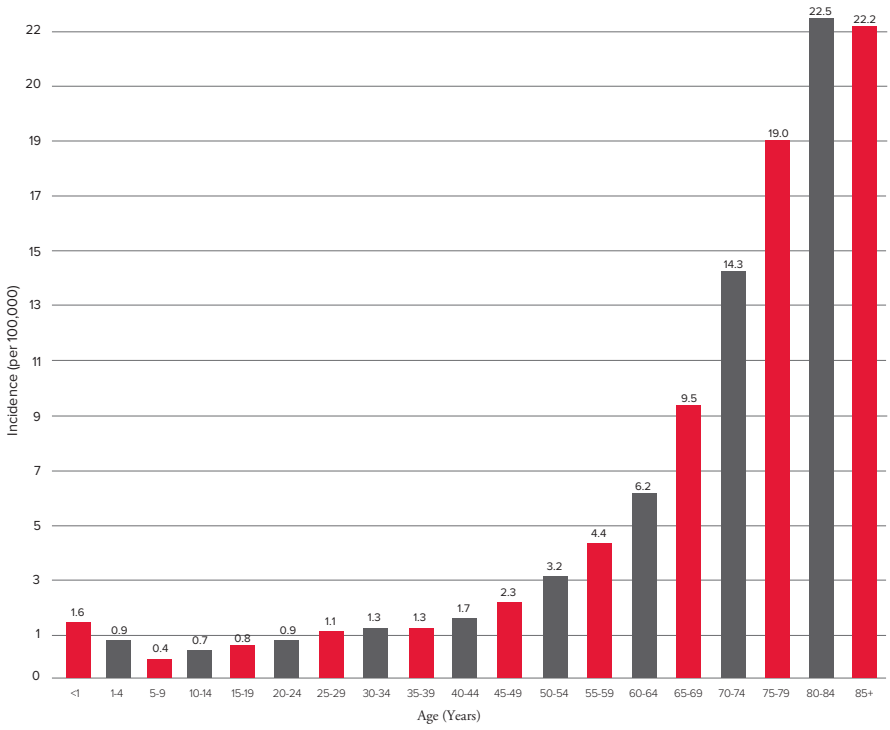

Figure 1. | The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of AML per 100,000 people in a given age-group. Source: SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, www.seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER website, 2011.

Signs and Symptoms. A person with signs or symptoms that suggest the possibility of leukemia is usually referred to a specialist. This may be a hematologist or an oncologist. The doctor will order additional tests to make a diagnosis (see page 9). The signs and symptoms of AML are associated with a number of other, less serious diseases.

It is common for people with AML to feel a loss of well-being because of the underproduction of normal bone marrow cells. The person may tire more easily and have shortness of breath during normal physical activities.

People with AML may also have

- A pale complexion from anemia
- Signs of bleeding caused by a very low platelet count, including
  - Black-and-blue marks or bruises occurring for no reason or because of a minor injury
  - The appearance of pinhead-sized red spots on the skin, called "petechiae"
  - Prolonged bleeding from minor cuts
- Mild fever
- Swollen gums
- Frequent minor infections, such as perianal sores
- Loss of appetite and weight loss
- Discomfort in bones or joints
- Enlarged spleen
- Enlarged liver.

Bleeding. A low platelet count predisposes patients to bleeding. Bleeding in the brain or lung is serious and can be fatal. However, such bleeding is usually preceded by minor bleeding, such as nose bleeds, blood in the urine or bruises (see *Disease and Treatment Side Effects* on page 23).

Infection. Severe infection can occur at the time of diagnosis but becomes more common and often more serious during treatment, when the bone marrow is completely suppressed. If the neutrophil count becomes or remains low because of AML or its treatment, serious infection almost invariably occurs and is a leading cause of death from AML (see *Disease and Treatment Side Effects* on page 23).

Myeloid Sarcoma. Rarely, a collection of AML cells, called a "myeloid sarcoma," forms outside the marrow. A myeloid sarcoma may occur in almost any part of the body. Other signs of AML may not appear in the blood and marrow until weeks or months after the initial myeloid sarcoma diagnosis. A myeloid sarcoma diagnosis is equivalent to a diagnosis of AML and is treated with chemotherapy rather than local therapy. Treatment may also include allogeneic or autologous stem cell transplant. Other names for a myeloid sarcoma are "chloroma," "granulocytic sarcoma," "myeloblastoma" or "monocytoma."

Diagnosis

An accurate diagnosis of the type of leukemia is important. The exact diagnosis helps the doctor to

- Estimate how the disease will progress
- Determine the appropriate treatment.

Talk to your doctor about

The diagnostic tests that are being done
What the results mean
Getting copies of the test results.

Some of these tests may be repeated during and after therapy to measure the effects of treatment.

Blood and Bone Marrow Tests. Blood and bone marrow tests are used to diagnose AML and the AML subtype. A change in the number and appearance of blood cells helps to make the diagnosis. AML cells look similar to normal immature white cells. However, their development is incomplete (see Figure 2).

Normal Marrow Cells and AML Blast Cells

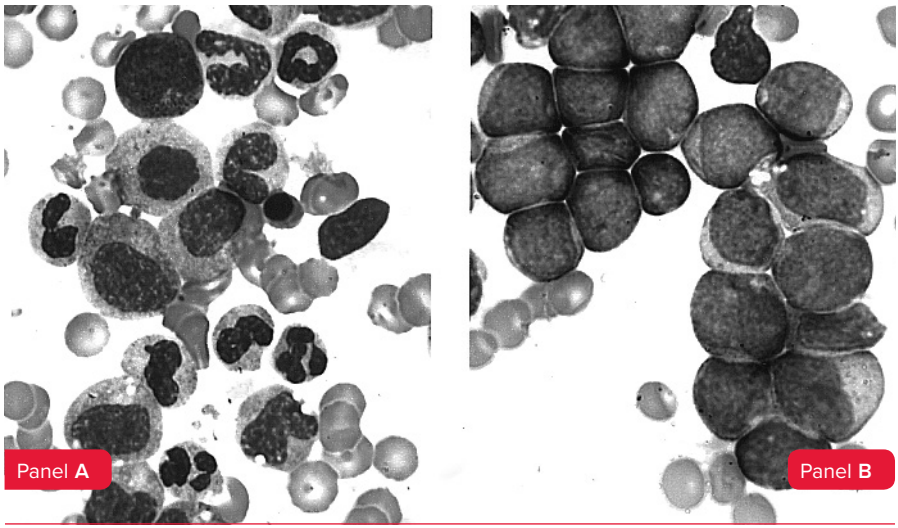

Figure 2. | **Panel A** shows normal marrow cells seen through a microscope. The darker shapes are the nuclei of the cells. Some of the nuclei are circular and some are horseshoe shaped, reflecting the different developmental stages and the different types of cells. **Panel B** shows AML blast cells seen through a microscope. These cells are "arrested" in an early stage of development. The AML cells in panel B all have a similar appearance, in contrast to the varied appearance of the normal cells in panel A.

Blood and Marrow Samples. To do the tests, blood samples are generally taken from a vein in the patient's arm. Samples of marrow cells are obtained by bone marrow aspiration and biopsy (see page 36). The cells from the blood and marrow samples are examined under a microscope.

Most patients with AML have	Blood tests used
Lower-than-expected red cell and platelet counts	**CBC** – Blood cell counts are determined by a blood test called a "complete blood count (CBC).
Too many immature white cells and too few mature white cells	**Peripheral Blood Smear** – A test called a "peripheral white cells blood smear" (an examination of the stained [dyed] blood cells with a microscope) usually shows the presence of leukemic blast cells (myeloblasts). These immature cells do not function like normal, mature white blood cells.

Confirmation of Diagnosis. In addition to looking at the number and appearance of the cells in the blood samples, your doctor will also order other tests to

- Confirm the diagnosis
- Identify the AML subtype
- Develop a treatment plan.

Your doctor will work with a hematopathologist to confirm the diagnosis. A hematopathologist is a specialist who studies blood cell diseases by looking at samples of blood and marrow cells and other tissues. The diagnosis of AML is confirmed by identifying

- Leukemic blast cells in bone marrow samples
- The percentage of blast cells. Blasts are normally 1 to 5 percent of marrow cells. Having at least 20 percent blasts is generally required for a diagnosis of AML. But AML can also be diagnosed if the blasts have a chromosome change that occurs in a specific type of AML, even if the blast percentage is less than 20 percent.
- Specific chemical activity in blast cells
- Characteristic markers (antigens) on the surface of blast cells, such as CD13 or CD33 (CD is an abbreviation for "cluster designation").
- Cells based on the types of markers (antigens) on the cell surface, a process called "immunophenotyping." "Flow cytometry" is the name of one test that may be used to do immunophenotyping.

Other Tests. "Karyotyping" and "cytogenetic analysis" are processes used to identify certain changes in chromosomes and genes. A laboratory test called "polymerase chain reaction (PCR)" may be done, in which cells in a sample of blood or marrow are studied to look for certain changes in the structure or function of genes, such as *FLT3* and *NPM1*.

AML Subtypes. Most people who are diagnosed with AML have one of the eight AML subtypes shown in Table 1. This table is based on the French, American, British (FAB) classification system that is used by many doctors. Treatment is similar for most of these subtypes, with the exception of M3—acute promyelocytic leukemia (APL). Treatment for APL is described on page 20.

Table 1. AML Subtypes[1]

Cell Subtype	Description
Myeloblastic	M0 – minimally differentiated AML
Myeloblastic, with minimal maturation	M1 – myeloblasts are the dominant leukemic cells in the marrow at the time of diagnosis.
Myeloblastic, with maturation	M2 – many myeloblasts, but some cells are developing toward fully formed blood cells.
Promyelocytic	M3 – leukemic cells have a translocation between chromosomes 15 and 17.
Myelomonocytic	M4 – leukemic cells often have a translocation or an inversion of chromosome 16.
Monocytic	M5 – leukemic cells have features of developing monocytes (white cells).
Erythroleukemic	M6 – leukemic cells have features of developing red cells.
Megakaryocytic	M7 – leukemic cells have features of developing platelets.

[1]Based on the FAB classification.

Table 1. | AML cells may have features of red cells, platelets or white cells (monocytes, eosinophils or, rarely, basophils or mast cells) in addition to myeloblasts or promyelocytes. When one cell line is dominant, the disease may be referred to as acute erythroid leukemia, acute megakaryocytic leukemia, acute monocytic leukemia and so forth.

The World Health Organization (WHO) classification system for AML is used by some doctors. It divides AML into several broad groups based on expected outcomes. The WHO classifications for AML include

- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
- Therapy-related AML
- AML not otherwise specified
- AML with a translocation between chromosomes 8 and 21
- AML with a translocation or inversion in chromosome 16
- AML with changes in chromosome 11
- Acute promyelocytic leukemia (APL, M3), which usually has a translocation between chromosomes 15 and 17.

Treatment

A diagnosis of AML is associated with a wide range of outcomes.

Treatment Planning. A number of factors affect the choice and outcome of treatment, including

- Your AML subtype
- The results of cytogenetic analysis
- Whether you have received chemotherapy in the past to treat another type of cancer
- Whether you have had myelodysplastic syndrome (MDS) or another blood cancer
- Whether the AML is in your central nervous system
- Whether your AML has not responded to treatment or has relapsed
- The presence of systemic infection at diagnosis
- Your age and general health.

Changes to Chromosomes and Genes. A bone marrow examination of the cytogenetic pattern and the status of the molecular markers, for example *FLT3* and *NPM1*, is important. Certain changes to the chromosomes and genes can provide important information for treatment planning. Normal human cells contain 23 pairs of chromosomes (22 numbered pairs and either XX for female or XY for male). About 60 percent of people with AML have abnormal chromosomes (number and/or structure). In some cases of AML, the cells have chromosome changes that can be seen under a microscope. Not all chromosome changes can be seen under a microscope. Other laboratory tests may be used to detect chromosome changes. Common AML chromosome changes include trisomy 8, trisomy 21, monosomy 7, monosomy 21 and loss of an X or Y chromosome. Genetic changes may occur in patients with normal chromosomes, so it is important for your doctor to do a molecular analysis (see Table 2 on page 13).

Table 2. Some AML Risk Factors

Certain chromosome and gene abnormalities, alone or in combination, may affect a patient's response to treatment. Researchers continue to work on developing better treatments for all patients.

Risk Group	Chromosomes[1] (Cytogenetic Analysis)	Genes (Molecular Analysis)
Most favorable	8;21 translocation (M2 subtype)	*RUNX1-RUNX1T1*
	15;17 translocation (M3 subtype, APL)	*PML-RARa* (APL)
	16;16 translocation or inversion 16 (M4 subtype)	*CBF-ßMYH11*
	No chromosome changes	*NPM1* or *CEBPA* mutation, without *FLT3-ITD*
Intermediate	No chromosome changes	
	9;11 translocation	*MLLT3-MLL*
	Other nondefined chromosome changes (fewer than 3 changes)	
	Trisomy 8 [2, 3]	
Least favorable	Deletion of all or part of chromosomes 5 and 7b	
	6;9 translocation	*DEK-NUP214*
	Inversion 3 or 3;3 translocation	*RPN1-EVI1*
	v;11q23 translocation	*MLL*-rearranged
	Monosomy 5, del(5q), monosomy 7	
	3 or more chromosome changes without one of the recurring translocations or inversions	
	No chromosome changes	*FLT3-ITD* with or without *NPM1* mutation ERG and BAALC overexpression

[1] Cytogenetic changes are sometimes abbreviated. For example:
- A translocation may be written as t(8;21)
- An inversion may be written as inv(16)
- A deletion may be written as del(7) or -7
- The letter "v" is an abbreviation used to indicate a variable chromosome. For example, an 11q23 translocation sometimes involves genes other than *MLL*.

See pages 33 to 50 for definitions of terms.

[2] Gene association not defined.

[3] Trisomy 8 is equally distributed among risk subgroups and does not affect risk in the absence of genetic changes. Impact of other genes such as *IDH1, IDH2* and *WT1* is under continued study.

High White Cell Count. About 5 percent of AML patients develop signs or symptoms attributable to a very high blood blast cell count. A white cell count greater than 100,000 at the time of diagnosis is associated with unfavorable risk.

Fast Facts About AML Treatment

- For some patients, AML is curable with current therapies.
- A person who has AML should (or must) be evaluated and treated by a hematologist or an oncologist.
- It is essential to seek treatment in a center where doctors are experienced in the care of patients with acute leukemia.
- Many patients with AML, particularly those with high white blood cell counts, need treatment as soon as possible after diagnosis. The approach for treating each patient is based on an individual's subtype, risk factors and treatment goals.
- Achieving a remission is important because it is associated with prolonging survival. The initial goal of treatment is usually to bring about a remission, in which
  - There is no evidence of leukemic blast cells in the blood or marrow.
  - Normal blood cell production is restored and blood cell counts return to normal levels.
- Variations on standard approaches to treatment are undergoing intensive study throughout the world. A patient may receive a different number of drugs, a different sequence of drugs, or drugs different from those described in this booklet, and still be receiving appropriate and effective treatment.
- In most patients, intensive chemotherapy is required to achieve complete remission. At least two drugs are combined to treat patients initially.
- More treatment is needed once a remission is achieved to help prevent a relapse.
- Postremission treatment may consist of chemotherapy, stem cell transplantation or low-dose maintenance chemotherapy.
- If relapse occurs, treatment options may include different chemotherapy regimens, allogeneic stem cell transplantation or other investigational therapies.
- For older AML patients, age alone is not a contraindication to treatment. Fit patients in their 70s and 80s can enter remission.
- Patients who have the M3 subtype, acute promyelocytic leukemia (APL), are treated with all-*trans* retinoic acid, arsenic trioxide and an anthracycline (see page 20).

Talk to your doctor about | Your treatment options and the results you can expect from treatment. It is important to be informed about the results you might expect with standard therapy and to discuss the possibility of participating in a clinical trial.

Chemotherapy. The initial phase of chemotherapy is called "induction therapy." Induction may involve the simultaneous use of multiple drugs or a planned sequence of treatments. For most AML subtypes, patients are treated with an anthracycline, such as daunorubicin, doxorubicin or idarubicin, combined with cytarabine (also called "cytosine arabinoside" or "ara-C"). Other drugs may be added or substituted for higher-risk, refractory or relapsed patients. Autologous or allogeneic stem cell transplantation may be added to the treatment plan for patients with relapsed AML or patients at high risk of relapse after chemotherapy (see page 18).

The anthracycline and cytarabine act in different ways to stop AML cell growth and lead to AML cell death. The anthracycline is usually given in the first 3 days of treatment. Cytarabine is started at the same time but is given for 7 to 10 days of treatment. This treatment is also called "7 plus 3." Both drugs are dissolved in fluids and given to the patient via an indwelling catheter (central line) or port. While "7 plus 3" is considered to be a standard, there are several clinical trials looking at ways to improve both the rate and duration of remission by adding specific molecularly-targeted drugs, increasing the doses of cytarabine and/or anthracyclines, or using a new drug that combines the cytarabine and anthracycline in a very specific ratio and delivers them together in an encapsulated form.

The central line is placed surgically in a vein in the upper chest. The catheter is tunneled under the skin of the chest so that it stays firmly in place. The external end of the port can be used to administer medications, fluids or blood products, or to withdraw blood samples for cell counts and chemical tests. See the free LLS booklet *Understanding Drug Therapy and Managing Side Effects* for additional information about drug administration.

Typically, the severity of the disease and the side effects of this initial therapy result in an initial hospital stay of 4 to 6 weeks. Some patients who live with a caregiver and near the medical facility may be safely discharged sooner. This depends on the policies of the treatment center and the status of the patient.

The goal of induction therapy is to rid the blood and marrow of visible leukemic blast cells. Generally, if blast cells are still evident after the first course of induction chemotherapy, a second course of the same chemotherapy is given. Table 3, on page 16, lists some of the standard drugs used to treat AML patients, as well as some of the drugs under study in AML clinical trials. Please check www.LLS.org or call our Information Specialists at (800) 955-4572 for updates to this information.

Table 3. Some Drugs Used to Treat Acute Myeloid Leukemia

Most antileukemic drugs interact with the cell's genetic material (the DNA).

Anthracyclines (Antitumor Antibiotics)

- daunorubicin (Cerubidine®)
- doxorubicin (Adriamycin®)
- idarubicin (Idamycin®)
- mitoxantrone (Novantrone®)

Antimetabolites

- cladribine (2-CdA; Leustatin®)
- clofarabine (Clolar®)
- cytarabine (cytosine arabinoside, ara-C; Cytosar-U®)
- fludarabine (Fludara®)
- hydroxyurea (Hydrea®)
- methotrexate
- 6-mercaptopurine (Purinethol®)
- 6-thioguanine (Thioguanine Tabloid®)

Topoisomerase Inhibitors

- etoposide (VP-16; VePesid®, Etopophos®)
- topotecan (Hycamtin®)

DNA Damaging (Alkylating) Agents

- cyclophosphamide (Cytoxan®)
- carboplatin (Paraplatin®)
- temozolomide (Temodar®)

Cell-Maturing Agents

- all-*trans* retinoic acid (ATRA, tretinoin; Vesanoid®)
- arsenic trioxide (Trisenox®)

Hypomethylating Agents

- azacitidine (Vidaza®)
- decitabine (Dacogen®)

Table 3. | This table lists some of the standard drugs and some of the drugs under study in clinical trials to treat AML patients. Various approaches to AML treatment are undergoing study in clinical trials. A patient may be treated with drugs that are not listed in this table and still be receiving appropriate and effective treatment. For a description of standard chemotherapy combinations, see page 15. It is essential to seek treatment in a center where doctors are experienced in the care of patients with acute leukemia.

Postremission Therapy. Normal blood cell production will return in many patients several weeks after initial treatment is completed. Blood cell counts gradually approach normal, well-being returns and any remaining AML cells cannot be detected in blood or marrow. This is called a "remission." A small number of residual AML cells will not interfere with normal blood cell development, but the number of cells has the potential to grow and cause a relapse of the AML.

Postremission therapy, also called "consolidation therapy," is needed to kill remaining AML cells and prevent relapse. Some of the main factors that influence the approach used include

- Patient age
- Ability to tolerate intensive treatment
- Cytogenetic and molecular characteristics of the AML cells
- Availability of an HLA-matched related or unrelated stem cell donor.

AML postremission treatment consists of additional intensive chemotherapy after remission has been achieved, with or without autologous or allogeneic stem cell transplantation. Patients are hospitalized for postremission therapy. The length of stay varies depending on the treatment and other factors.

Patients who do not have a transplant generally are given four cycles of chemotherapy. If chemotherapy alone is used, the best results occur if intensive treatment is applied. Intensive chemotherapy can be given with high dosages of cytarabine or other drugs.

Some patients may benefit from intensive chemotherapy alone followed by one of three types of stem cell transplantation:

- Autologous
- Allogeneic
- Reduced-intensity allogeneic (under study in clinical trials).

The question of which patients are likely to benefit from transplantation after their first complete remission is under study in clinical trials. Studies show that allogeneic stem cell transplantation may benefit poor- and intermediate-risk patients who are younger than 60 and have a sibling match. There does not seem to be any clear advantage for patients considered favorable or chemo-sensitive. Autologous transplant is being used in some centers as an alternative to multiple cycles of chemotherapy. Treating with a reduced-intensity transplant has shown some benefit for healthier older patients, up to age 75.

Clinical trials are examining several different approaches: modulating the activity of the immune system (e.g. vaccines or cytokines) or giving new drugs that differ from standard chemotherapy (e.g. tipifarnib [Zarnestra®], sorafenib [Nexavar®],

azacitidine [Vidaza®], lenalidomide [Revlimid®]). Various forms of less intensive maintenance treatment such as the role of hypomethylating agents or azacitidine and decitabine, after completion of postremission chemotherapy, are also under study in clinical trials.

Autologous Stem Cell Transplantation. Autologous transplantation is relatively safe for many patients, including older patients. For some AML patients who do not have an HLA-matched stem cell donor, therapy can be further intensified with very-high-dose chemotherapy followed by an autologous transplant. This procedure uses the patient's own stem cells to restore blood cell production after intensive chemotherapy.

Talk to your doctor about | The potential benefits and risks of this procedure.

For more information, see page 34 and the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Allogeneic Stem Cell Transplantation. Allogeneic stem cell transplantation is used to treat certain AML patients. It is a curative treatment option for some AML patients in first remission.

The upper age limit for transplantation varies by treatment center; many centers use age 60 or 65 years for allogeneic transplantation and 70 years for reduced-intensity allogeneic transplantation.

Patients in these age ranges who are in remission and have an HLA-matched stem cell donor may be candidates for this procedure. Umbilical cord blood, like bone marrow and peripheral blood, is a rich source of stem cells for transplantation. It is an alternative source for donor stem cells if an appropriate sibling or unrelated donor is not available.

Allogeneic transplantation is associated with a higher rate of side effects and mortality than autologous transplant. However, it may be considered for patients with worse-risk AML, based on cytogenetic and molecular test results. The decision to perform an allogeneic transplant also depends on the age of the patient and the patient's (or his or her family's) understanding of the potential benefits and risks. As one example, a younger patient with cytogenetic and molecular findings that are associated with a high probability of relapse would be a candidate for allogeneic stem cell transplantation early in treatment if he or she had a stem cell donor. Alternative therapies include intensive consolidation chemotherapy, reduced-intensity transplantation or autologous transplantation.

Reduced-Intensity Stem Cell Transplantation. Reduced-intensity allogeneic stem cell transplantation may be a treatment option for patients who are too old or

ill to have an allogeneic stem cell transplant (based upon other medical conditions or general health status), if a suitable donor is available. The conditioning therapy used for a reduced-intensity transplant is of lower intensity than that for a standard stem cell transplant; it does not completely inactivate the patient's immune system or treat the AML as intensively.

Reduced-intensity allogeneic stem cell transplantation is based on two considerations:

- Much-improved immunosuppressive therapy prevents the patient from rejecting the donor's stem cells, even though the patient's immune system has not been fully suppressed by the lower-intensity conditioning therapy
- The anticipated attack of the donor's immune cells successfully suppresses the patient's leukemia cells. This attack is referred to as "graft-versus-tumor effect" (graft-versus-leukemia effect or GVL). Over time, if the transplant is successful, the donor's stem cells replace the patient's immune cells. The engrafted donor immune cells recognize minor tissue antigens on the patient's leukemia cells and continue to suppress their growth.

The risks and benefits of this treatment have not yet been clearly established. As is the case with allogeneic stem cell transplantation, the risk of graft-versus-host disease (GVHD) is an important consideration and a potentially disabling side effect.

Talk to your doctor about | Whether a reduced-intensity transplant is a potential option for you.

See the free LLS publications *Blood and Marrow Stem Cell Transplantation* and *Cord Blood Stem Cell Transplantation* for comprehensive information about allogeneic stem cell transplantation.

Central Nervous System (CNS) AML. CNS disease occurs in approximately 1 in 50 cases at the time of diagnosis. Preventive therapy is usually not indicated for CNS AML, but examination of the spinal fluid after remission should be considered for patients with

- Monocytic subtypes
- Masses of AML cells outside the marrow
- Inversion 16 and 8;21 translocation
- CD7- and CD56-positive (neural-cell adhesion molecule) immunophenotypes
- Very high blood blast-cell counts at diagnosis.

Refractory Leukemia and Relapsed Leukemia. Most patients achieve an initial remission. However, some patients have residual leukemic cells in their marrow even

after intensive treatment. This is referred to as "refractory leukemia." There are other patients who have a return of leukemia cells in the marrow and a decrease in normal blood cells after achieving a remission. This is referred to as "relapsed leukemia."

With refractory leukemia, approaches such as using drugs not used in the first course of treatment may be taken in an effort to induce remission. Stem cell transplantation may be used when remission is achieved, which may result in a more durable remission. In patients who relapse, the duration of the remission, the patient's age and the cytogenetic findings in the leukemia cells influence the approach to therapy. Drugs similar to those administered initially, different drugs or stem cell transplantation may be used to treat the leukemia.

The Information Specialists at LLS offer guidance on how patients can work with their doctors to find out if a specific clinical trial is an appropriate treatment option. Information Specialists conduct clinical-trial searches for patients, family members and healthcare professionals. You can use the LLS-supported online tool TrialCheck® at www.LLS.org/clinicaltrials, a clinical-trial search service that offers patients and caregivers immediate access to listings of blood cancer clinical trials.

Transplantation in Relapsed Patients. Some form of allogeneic transplantation may be recommended for patients in early first relapse or second remission. For patients who lack a sibling donor, matched-unrelated donor transplants can be effective, although this is a high-risk procedure. Patients with AML who relapse after allogeneic stem cell transplantation may have a long-term remission if they have a second transplant. Donor leukocyte infusion is sometimes used to treat patients with AML relapse after transplant. This therapy is most effective in early relapses and in the absence of extensive chronic graft-versus-host disease (GVHD).

Talk to your doctor about	Therapies under study in clinical trials if you have refractory or relapsed AML.

Several drugs and drug combinations that can be used to treat AML are being studied in clinical trials. For more information about specific clinical trials for relapsed and refractory leukemia, go to www.LLS.org/clinicaltrials or contact our Information Specialists.

Acute Promyelocytic Leukemia (APL) Treatment. APL is the M3 subtype of AML (see Table 1 on page 11). Patients with APL are among the most frequently cured. APL treatment differs from the other AML treatments described in this booklet.

With APL, the cells that accumulate in the marrow can be identified as promyelocytes, the step in blood cell formation that comes after the development of myeloblasts. These cells also have a specific chromosome abnormality involving chromosome 15, usually in conjunction with chromosome 17.

All-*trans* retinoic acid (ATRA), a vitamin A derivative, is a standard component of induction therapy for APL. ATRA is also known as tretinoin (Vesanoid®). Retinoic acid is capable of inducing the leukemic promyelocytes to develop into mature cells (neutrophils). It causes a marked decrease in the concentration of leukemic blast cells in the marrow, and a remission frequently follows.

Used alone, ATRA can induce a short-term remission in at least 80 percent of patients. Treatment with ATRA must be followed by or given with chemotherapy in order for the remission to be long-lasting. ATRA often minimizes the side effects of chemotherapy because blood cell counts may be improved and the number of leukemic cells may be decreased at the time that chemotherapy is started.

The remission rate of APL patients treated with ATRA and an anthracycline, such as idarubicin, is about 70 to 80 percent. Nevertheless, problems with hemorrhage during the initial phases of treatment, resistance to treatment and relapse occur in a proportion of patients, as they do in some patients with other types of AML. Therefore, long-term follow-up of patients in remission is required to identify those who are cured and those who may require further therapy.

For APL patients with a white cell count of 10,000/μL or greater at diagnosis, cytarabine may be added to induction or consolidation regimens.

The ideal duration of maintenance therapy is also being investigated. Currently, it consists of 2 years of 6-mercaptopurine (6-MP), methotrexate, and ATRA.

A small number of APL patients have persistent minimal residual disease (MRD) at the end of consolidation therapy. These patients may benefit from arsenic trioxide (Trisenox®), followed by allogeneic stem cell transplantation, if an HLA-matched donor is available.

Patients who do not have a donor, or cannot have an allogeneic stem cell transplant for other reasons, may be candidates for an autologous stem cell transplantation. Arsenic trioxide is approved to treat APL patients who have relapsed or are resistant to treatment with chemotherapy and ATRA.

See page 30 for an example of a treatment under study in clinical trials.

Acute Monocytic Leukemia Treatment. In some types of leukemia, including the subtype of monocytic leukemia (M5; see Table 1 on page 11), the leukemic blast cells sometimes invade the lining of the spinal cord or brain. This does not usually occur with other types of acute myeloid leukemia. When the lining of the spinal cord or brain is involved, chemotherapy is injected into the spinal fluid. A lumbar puncture (also known as a "spinal tap") is a commonly used medical procedure, performed under local anesthesia or with heavy sedation. During a lumbar puncture, a needle is placed into the spinal canal and the spinal fluid is removed and examined for leukemia cells. The extracted fluid volume is then replaced with fluid containing appropriate drugs, usually cytarabine or methotrexate.

AML Treatment in Older Adults. Acute myeloid leukemia occurs more frequently with advancing age. At least half of patients are older than 65 years of age when the disease is diagnosed. Today there are curative options available for some older patients, including those who may have other significant health issues.

For AML patients older than 60 years, patient performance status, other health issues and AML risk features are all considered in developing a treatment plan. Age alone is not a contraindication to treatment, and fit patients in their 70s and 80s can enter remission. Standardized measures of strength and reaction time are used to determine physiological age, which is a better indicator of tolerance for therapy. However, older patients may have a poorer response to therapy because

- The leukemic cells of older AML patients have a higher occurrence of unfavorable cytogenetic and molecular abnormalities.
- Older patients may have other medical problems (called "comorbidities"), including heart, lung or kidney disease or diabetes mellitus. The doctor may have to select less toxic AML drugs or decrease the dosage and frequency of treatment.

It is important to know that even in otherwise healthy patients aged 75 years or older, the principal cause of treatment failure is not toxicity, but failure of the treatment to eliminate the AML cells.

Treatment for older adults can be tailored to decreased tolerance if needed. Azacitidine (Vidaza®) and decitabine (Dacogen®) are low-intensity treatment options. Vidaza and Dacogen are approved to treat patients with certain types of myelodysplastic syndromes (MDS) and are being studied in clinical trials for the treatment of patients with AML. There are diverse clinical trials looking at novel drugs and combinations for the treatment of AML in the elderly. Examples include tipifarnib (Zarnestra®), CPX-351, bortezomib (Velcade®), lenalidomide (Revlimid®), clofarabine (Clolar®) and the combination of azacitidine (Vidaza®) or decitabine (Dacogen®) with other "gene-expression modifying" agents (entinostat, vorinostat [Zolinza®], valproic acid [Depakene®; Stavzor®]).

Occasionally, very elderly patients refuse treatment or are so ill from unrelated illnesses that treatment may be unreasonable.

Talk to your doctor about | Whether treatment in a clinical trial is right for you.

AML Treatment in Children. Most children who are diagnosed with leukemia have acute lymphoblastic (lymphocytic) leukemia. Acute myeloid leukemia accounts for about 15 to 20 percent of cases of acute childhood leukemia.

Children who have AML are treated with an induction therapy similar to that for adults with AML: cytarabine and drugs such as doxorubicin or daunomycin, or a third drug, such as mitoxantrone. This treatment is followed by a complex multidrug program that results in about an 80 percent remission rate and a nearly 50 percent 5-year, relapse-free remission rate. Slightly more than half of the children in relapse-free remission are considered cured. Infants are usually treated with the same therapy.

Children less than 2 years of age who have AML have a decreased rate of remission and cure. In addition, the AML subtype acute monocytic leukemia (see page 11 and page 21) and a very-high-blast-count leukemia called "hyperleukocytic leukemia" are variants of AML that are much more difficult to treat, with lower remission and cure rates than the average results noted above.

Allogeneic stem cell transplantation (see page 18) may be used to treat children who have

- Worse risk, based on cytogenetic and molecular test results
- Primary induction failure
- Relapse after intensive multidrug therapy.

Clinical Trials for Childhood AML. AML is one of the most challenging childhood cancers to treat. Multi-institution clinical trials are under way to determine the best treatments for worse-risk patients. The expected outcomes for children who have AML with cytogenetic or molecular abnormalities may be different from those for adults who have the same abnormalities.

Chemotherapy has been used in different combinations and dosages over the past several decades, leading to improved childhood AML cure rates, but more research is needed to further improve cure rates and decrease the side effects and long-term and late effects of chemotherapy.

Researchers have identified cell targets that appear to be the key to treatment with the new generation of chemotherapy agents. These new targeted agents are being studied in conjunction with chemotherapy to examine their impact upon cure rates and their effect on toxic complications associated with traditional chemotherapy. Researchers are also studying risk factors and treatments for AML chemotherapy complications, especially infections, to make AML therapy safer for children.

See the free LLS booklet *Learning & Living with Cancer: Advocating for your child's educational needs* for information about planning for the child's entry or return to school following diagnosis and treatment.

Disease and Treatment Side Effects. Most AML side effects are temporary and subside once the body adjusts to therapy or when therapy is completed. During the course of therapy and after therapy is completed, healthy new cells begin to grow and develop. Severe side effects are treated on an inpatient basis.

Low Blood Cell Counts. AML decreases the production of normal blood cells. In addition, chemotherapy is toxic to both normal blood cells and AML cells. The normal blood cells are eliminated from the marrow along with AML cells. For the patient, this results in a severe deficiency in the

- Red cells (anemia)
- Platelets (thrombocytopenia)
- White cells called "neutrophils" and "monocytes" (neutropenia and monocytopenia).

Transfusion of red cells and platelets is almost always needed for a period of several weeks during treatment. After that, the blood cell counts usually return toward normal.

Infection. During treatment for AML, the deficiency of neutrophils and monocytes (types of white cells) can lead to infection from bacteria and fungi normally present in the environment, on the skin and in the nose, mouth or colon. The risk of infection may be increased because chemotherapy damages the lining of the mouth and intestines, making it easier for bacteria to enter the blood. When the white cell count is low and infection risk is increased, antibiotics are given to prevent or treat infection. Transfusion is not generally used for patients with a low neutrophil count, but can be used in patients with high fever, infection that is unresponsive to antibiotics, blood fungal infections or septic shock.

Growth factors may be given to the patient to stimulate the marrow to make new white cells. The growth factors used most frequently are G-CSF (granulocyte colony-stimulating factor; filgrastim [Neupogen®] and pegfilgrastim [Neulasta®]) and GM-CSF (granulocyte-macrophage colony-stimulating factor; sargramostim [Leukine®]). These agents are used in children only in special circumstances.

Because the patient has an increased risk of developing an infection, the medical staff and family and friends need to practice frequent and vigorous hand washing and take other precautions to avoid exposing patients to bacteria, viruses and other infection-causing agents. Caregivers for patients with central lines or ports need to be meticulous in the cleaning of catheters.

Patients at home should not delay in seeking medical attention if any signs of infection develop. A rise in temperature to 101°F or higher, or the onset of chills, may be the only sign of infection in a patient with a very low white cell count. Other signs of infection may include persistent coughing; tenderness at a site prone to infection, such as the area surrounding the anus or the facial sinuses; sore throat; pain on urination; or frequent loose stools.

Other Side Effects. Chemotherapy affects tissues that normally have a high rate of cell turnover. Thus, the lining of the mouth, the lining of the intestines, the skin and the hair follicles may be affected. Common side effects may include

- Mouth ulcers
- Diarrhea
- Temporary hair loss
- Rashes
- Nausea and vomiting
- Fatigue.

Some AML patients may build up uric acid in their blood as a result of a very high white cell count. The use of chemotherapy may also increase uric acid, which is a chemical in the cell. Uric acid enters the blood and is excreted in the urine. If many cells are killed simultaneously by therapy, the amount of uric acid in the urine can be so high that kidney stones can form. This may seriously interfere with the flow of urine. Drugs such as allopurinol (Zyloprim®) or rasburicase (Elitek®) can be given to minimize the buildup of uric acid in the blood.

There are drugs and other supportive therapies to prevent or manage many side effects. For more information see the free LLS publications *Blood Transfusion, Cancer-Related Fatigue Facts* and *Understanding Drug Therapy and Managing Side Effects*.

Sometimes, a drug or a drug combination causes effects that continue for a period of time after treatment ends. Some effects may be long-lasting (see *Long-Term Effects of Treatment* on page 26).

Talk to your doctor about | Possible side effects and follow-up care.

Follow-up Care. Some of the tests that were done to diagnose AML may be repeated to

- Follow the effects of treatment
- Make decisions about whether to continue, intensify, change or stop treatment.

After treatment, patients who are in remission and have completed postremission therapy continue to be examined regularly by their doctors. Careful periodic

assessment of the patient's health, blood cell counts and, if indicated, marrow is required. As time progresses, the length of time between assessments may grow, but assessments should continue indefinitely.

Long-Term Effects of Treatment. Children and young adults who have been treated for AML may be at increased risk for heart damage, other cancers and neurologic or cognitive problems. Patients should be seen by a primary care physician for general health examinations at least once a year. They should also be examined regularly by an oncologist.

It is important to know about the potential for long-term effects of treatment so that any problems can be identified early and managed. Treatment for individuals who have AML sometimes causes effects that continue after treatment ends (long-term effects) or develop much later in life (late effects). Various factors can influence the risk of developing long-term or late effects, including

- Type and duration of treatment
- Age at the time of treatment
- Gender and overall health.

Most AML patients are treated with an anthracycline, such as daunorubicin. Anthracyclines have been associated with increased risk for heart muscle injury or chronic heart failure. Heart disease may not become apparent until many years after therapy ends.

Stem cell transplantation is used to treat some patients with AML. It has been associated with long-term or late effects, including infertility, thyroid dysfunction, chronic fatigue and risk for developing a second cancer (lymphoma; melanoma of the skin; or cancer of the tongue and salivary glands, central nervous system, bone, soft tissue and thyroid gland). The number of patients who develop secondary cancers is small.

These and other possible long-term and late effects can be managed. For more information see the free LLS fact sheets *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma* and *Long-Term and Late Effects of Treatment in Adults*.

Talk to your doctor about | Possible long-term effects and follow-up care.

Treatment Outcomes. Patients with AML have a difficult disease to cure. However, a few decades ago almost no adults with AML were cured. Today, advances in AML treatment have resulted in improved remission and cure rates.

Terms for AML Treatment Outcomes

Active disease	AML is still present during treatment or after treatment (refractory) or AML has come back after treatment (relapsed). A patient with AML that has relapsed has more than 5 percent blast cells present in the marrow.
Minimal residual disease	No AML cells are detected in bone marrow using standard tests, such as looking at cells under a microscope. But more sensitive tests, such as flow cytometry, or very sensitive tests, such as polymerase chain reaction (PCR), detect remaining AML cells in the marrow.
Complete molecular remission	No evidence of AML cells in the marrow when using very sensitive tests such as PCR.
Remission	No evidence of disease after treatment, (complete based on remission) ○ Less than 5 percent blast cells in the marrow ○ Blood cell counts within normal limits ○ No signs or symptoms of the disease.

Sensitive molecular techniques permit the identification of small amounts of cells (minimal residual disease [MRD]) that cannot be detected by standard tests of the patient's blood and marrow. This approach can be used if the leukemia cells have a detectable molecular abnormality. This feature can permit more sensitive follow-up of patients who are in remission and can help determine whether additional treatment is necessary. It is worth noting that, after treatment, a finding that 1 to 5 percent of the white cells in a patient's marrow are blast cells is not an indication of MRD. This percentage of blast cells may be found in persons who do not have leukemia.

Age is one of the main determinants of AML cure rate. Children with the disease have a cure rate just below 50 percent. Younger adults and patients with certain cytogenetic patterns and with certain subtypes, such as APL, have a greater possibility of cure. Allogeneic stem cell transplantation can cure some patients.

Relative survival compares the survival rate of a person diagnosed with a disease to that of a person without the disease. Based on data posted to the SEER website in April 2011, the overall AML 5-year relative survival rates for 2001-2007, by age at diagnosis, are as follows:

- Patients diagnosed with AML before age 65 have a 5-year relative survival rate of 39.6 percent
- Children less than 15 years of age have a total averaged 5-year relative survival rate of 60.9 percent
- Patients diagnosed at age 65 and older have an overall 5-year relative survival rate of 5.2 percent.

Figure 3 shows additional 5-year relative survival by age data. Note that these numbers do not take into account differences by gender, race and subtype of AML; the patient's risk based on cytogenetic and molecular test results; or the most recent advances in therapy and supportive care.

Acute Myeloid Leukemia: 5-Year Survival Rates (2001-2007)

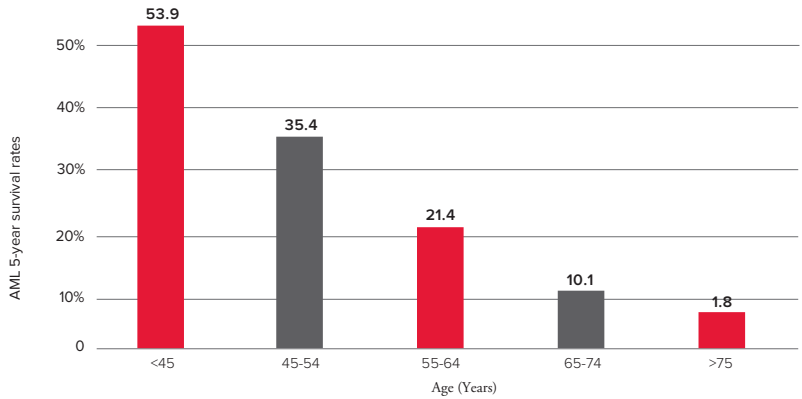

Figure 3. | Source: SEER Cancer Statistics Review, National Cancer Institute. 2011.

For more information about survivorship, including follow-up care, contact our Information Specialists at LLS.

Research and Clinical Trials

The proportion of patients with AML who enter remission, stay in remission for years or are cured has increased during the last 30 years. However, AML is still one of the most difficult cancers to treat. The challenge remains to develop treatments that cure patients of all ages and with all subtypes of AML. LLS invests research funds in both basic and applied-research programs to improve the cure rate for AML patients.

Fast Facts About Clinical Trials

- Studies of new treatments in clinical trials are conducted under rigorous guidelines to help doctors find out if new cancer treatments are safe and effective or better than the standard treatment.
- Patients in cancer clinical trials usually receive either the study treatment or the best standard treatment.
- Clinical trials take place throughout the United States and Canada and around the world.
- Many of today's standard treatments for cancer are based on earlier clinical trials.
- Taking part in a clinical trial may be the best treatment choice for some AML patients.
- There are some clinical trials for patients at every stage of treatment and for patients in remission.
- Our Information Specialists at LLS offer guidance on how patients can work with their doctors to find out about specific clinical trials. This service can be accessed by calling (800) 955-4572 or visiting www.LLS.org/clinicaltrials.
- To learn more about clinical trials, read the free LLS booklet *Understanding Clinical Trials for Blood Cancers* and visit www.LLS.org.

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

LLS Information Specialists, at (800) 955-4572, can offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct individualized

clinical-trial searches for patients, family members and healthcare professionals. This service is also available at www.LLS.org/clinicaltrials

Research Approaches. There are clinical trials for newly diagnosed patients and patients with relapsed or refractory disease. A number of approaches are under study in clinical trials for the treatment of patients with AML, as follows:

- A concept called "epigenetics" is based on the idea that certain genes become silenced (or turned off), which contributes to causing or maintaining cancer. Drugs that can reverse the silencing process are being studied in clinical trials, either alone or in combination with other drugs.
  - One process that leads to gene silencing is called "methylation," and there are two drugs that inhibit the process: azacitidine (Vidaza®) and decitabine (Dacogen®).
  - Another mechanism of gene silencing is called "histone deacetylase inhibition." Histone deacetylases attack silenced genes differently than methylation. Histone deacetylase inhibitors under study in clinical trials include valproic acid, suberoylanilide hydroxamic acid (SAHA) and entinostat. These drugs are being studied in combination with Vidaza or Dacogen.
- There are novel drugs that kill cells by triggering new pathways that cause cell death and thereby overcome resistance. The novel drugs may be combined with standard AML drugs such as ara-C and daunorubicin. Some novel drug examples are clofarabine (Clolar®), which is approved to treat acute lymphoblastic leukemia; vosaroxin (which is being studied in combination with cytarabine for relapsed/refractory AML); tipifarnib (Zarnestra®); flavopiridol; interleukin-2 (IL-2) with histamine dihydrochloride (Ceplene®); and a class of drugs called "antisense molecules." New drugs that target *FLT-3-ITD* include midostaurin, sorafenib (Nexavar®) and AC220. These drugs are being combined with other chemotherapy drugs. CPX-351 is a treatment currently being studied in newly diagnosed older adults and in relapsed/refractory adults.
- Another concept called "differentiation therapy" involves studying the use of all-*trans* retinoic acid (ATRA), which is approved to treat APL, and some types of histone deacetylase inhibitor drugs to promote the growth and differentiation of immature leukemic blast cells.
- Donor lymphocyte infusion after transplantation, vaccine therapy and other immunotherapies.

We encourage you to contact our Information Specialists and visit www.LLS.org for more information about specific treatments under study in clinical trials.

Normal Blood and Marrow

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

- Proteins
  - Albumin, the most common protein in blood
  - Blood-clotting proteins, made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red cell production
  - Immunoglobulins, antibodies made by plasma cells in response to infections including those we develop from our vaccinations (such as poliovirus antibodies, which are made by normal plasma cells in the bone marrow)
- Hormones (such as thyroid hormone and cortisol)
- Minerals (such as iron and magnesium)
- Vitamins (such as folate and vitamin B_{12})
- Electrolytes (such as calcium, potassium and sodium).

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

- The red cells make up a little less than half the volume of the blood. They are filled with hemoglobin, the protein that picks up oxygen in the lungs and delivers it to the cells all around the body; hemoglobin then picks up carbon dioxide from the body's cells and delivers it back to the lungs, where it is removed when we exhale.
- 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 a person has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the vessel, clump together and plug up the bleeding site with the help of blood-clotting proteins such as fibrin and electrolytes such as calcium. Later, a firm clot forms. The vessel wall then heals at the site of the clot and returns to its normal state.
- The neutrophils and monocytes are white cells. They are called "phagocytes" (eating cells) because they can ingest bacteria or fungi and kill them. Unlike the red cells and platelets, the monocytes can leave the blood and enter the tissue, where they can attack the invading organisms and help combat infection. Eosinophils and basophils are types of white cells that respond to allergens or parasites.
- Most lymphocytes, another type of white cell, are found in the lymph nodes, the spleen and the lymphatic channels, but some enter the blood. There are three major types of lymphocytes: T lymphocytes (T cells), B lymphocytes (B cells) and natural killer (NK) cells. Each of these cells is a key part of the immune system.

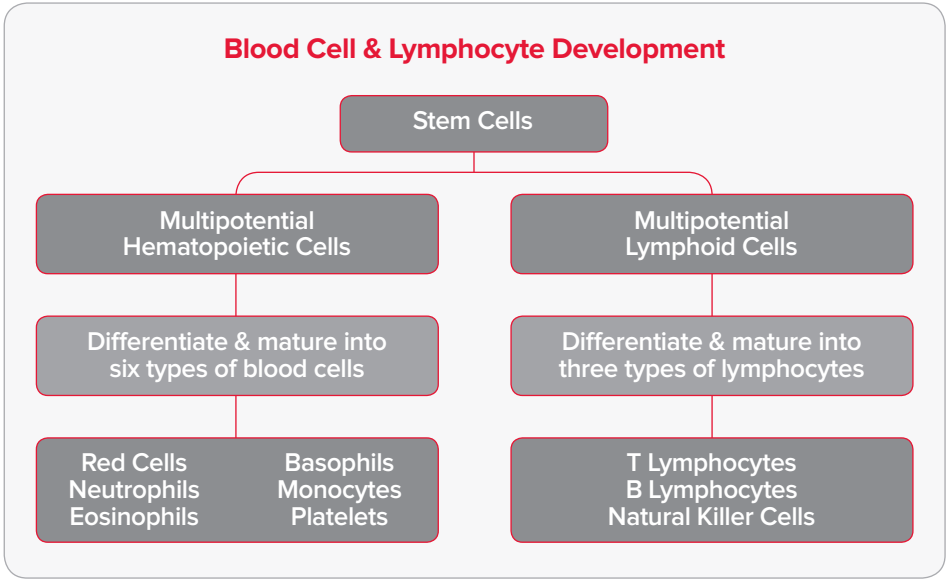

Figure 4. | **Stem cells** develop into blood cells (hematopoiesis) and lymphocytic cells.

Marrow is a spongy tissue where blood cell development takes place. It occupies the central cavity of bones. In newborns, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have functioning marrow. In adults, the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull contain the marrow that makes blood cells. The process of blood cell formation is called "hematopoiesis." A small group of cells, the stem cells, develop into all the blood cells in the marrow by the process of differentiation (see Figure 4).

In healthy individuals, there are enough stem cells to keep producing new blood cells continuously. Blood passes through the marrow and picks up the fully developed and functional red and white cells and platelets for circulation in the blood.

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. There are also methods to induce more stem cells to leave their home in the marrow and circulate in the blood, allowing a greater number of stem cells to be collected. If enough stem cells are harvested from a compatible donor, they can be transplanted into a recipient.

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

Medical Terms

Absolute Neutrophil Count (ANC). The number of neutrophils (a type of white cell) that a person has to fight infection. It is calculated by multiplying the total number of white cells by the percentage of neutrophils. People who have AML may have a low or normal absolute neutrophil count, depending on the total white cell count.

Alkylating Agent. A type of chemotherapy used to kill cancer cells by interfering with cancer cell division. Alkylating agents cause side effects because they also interfere with cell division in certain healthy tissues where cell division is frequent, such as the gastrointestinal tract. Cyclophosphamide is one of several types of alkylating agents.

Allogeneic Stem Cell Transplantation. A treatment that uses donor stem cells to restore a patient's marrow and blood cells. First, the patient is given conditioning therapy (high-dose chemotherapy or high-dose chemotherapy with total body radiation) to treat the blood cancer and to "turn off" the patient's immune system so that the donor stem cells will not be rejected. A type of transplant called a "reduced-intensity" or "nonmyeloablative" transplant is under study. It uses lower doses of conditioning therapy and may be safer, especially for older patients. For more information see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Anemia. A decrease in the number of red cells and, therefore, the hemoglobin concentration of the blood. The blood is less able to carry oxygen as a result. If severe, anemia can cause a pale complexion, weakness, fatigue and shortness of breath on exertion.

Anthracyclines (Antitumor Antibiotics). Chemotherapy agents that interact directly with the DNA in the nucleus of cells, thus interfering with cell survival.

Antibodies. Proteins released by plasma cells (derived from B lymphocytes) that recognize and bind to specific foreign substances, called "antigens." Antibodies coat, mark for destruction or inactivate foreign particles such as bacteria, viruses and harmful toxins. Antibodies can also be made in the laboratory in two ways. The first way takes advantage of the fact that if material is injected from one species into a different species, the latter will recognize it as foreign and make antibodies to attack it. These antibodies are usually polyclonal antibodies; that is, they react to multiple targets (antigens). The second way involves monoclonal antibodies, which react to only one target (antigen) and can be used in several important ways. They can be used to identify and classify types of blood cancers or be altered so as to become useful in antibody-mediated immunotherapy.

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

Antimetabolites. Chemotherapy agents that are generally similar to natural building blocks of DNA, RNA or some vitamins. However, they are changed from the natural chemical. When they substitute for the DNA or RNA building blocks within a leukemic cell, the cell is unable to form normal DNA or RNA. This prevents the cell from growing.

Antioncogene. See Tumor Suppressor Gene.

Apheresis. The process of removing components of a donor's blood and returning the unneeded parts to the donor. The process, also called "hemapheresis," circulates blood from a donor through a filter-type apparatus, and then back to the donor. Apheresis makes it possible to remove desired elements from large volumes of blood. Platelets, red cells, white cells and plasma can be removed separately. For example, this technique permits the harvest of enough platelets for transfusion from one donor (rather than six to eight separate donors). In this way, the recipient of the platelets is exposed to 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, which can be frozen and stored for later use in transplantation.

Autologous Stem Cell Transplantation. A technique used to delay the progression of certain blood cancers. The autologous transplantation process (or autotransplant) takes place after the patient achieves a complete response (remission), or a good partial response, to induction drug therapy. The process is as follows: 1) the patient's stem cells are harvested, usually from the blood; 2) the stem cells are frozen for later use and the patient receives conditioning drug therapy; 3) the stem cells are thawed and infused back to the patient through an indwelling catheter (central line). The main adverse side effects of the transplant are the results of the conditioning therapy; these include mouth sores, hair loss, nausea, vomiting, diarrhea and risk of infections. Patients receive supportive care to help prevent and/or manage the side effects. Generally, after 10 to 14 days, blood counts begin to normalize and the side effects of the conditioning therapy begin to resolve.

Autosomes. See Karyotype.

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

Biomarkers. Chemicals or structures present either on the surface of or within cells or in the serum. They may aid doctors in determining when treatment (and which type of treatment) is needed by identifying disease that will progress more rapidly and/or have a better or worse response to certain treatments. Examples of biomarkers are gene expression, serum protein levels and chromosome

abnormalities in cancer cells. No single feature can accurately predict disease progression in a patient; therefore, doctors use a combination of factors to make a diagnosis and a treatment plan. Biomarkers are also known as "cancer cell markers" and "tumor markers."

Biopsy. A procedure to obtain tissue for diagnosis. In many cases, a special needle can be used to obtain the tissue. In some cases, a larger piece of tissue may be surgically removed. Since the appearance of a lymph node is important in categorizing the type of lymphoma that may be present, surgical removal of one or more entire, swollen lymph nodes may be necessary (lymph node biopsy). The tissue is placed in preservative, stained with dyes and examined under a microscope by a pathologist.

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 lymphoblasts; that is, cells that are part of lymphocyte development. In the acute types of leukemia, blast cells similar in appearance to normal blast cells accumulate in large numbers, constituting up to 80 percent of all marrow cells. In myelodysplastic syndromes and acute myeloid leukemia, myeloblasts accumulate, and in acute lymphoblastic leukemia, lymphoblasts accumulate. Normal myeloblasts give rise to granulocytes (neutrophils, eosinophils and basophils). With myelodysplastic syndromes, abnormal myeloblasts displace or otherwise interfere with the production of normal red cells, white cells and platelets in the marrow. Sometimes the distinction between myeloblasts and lymphoblasts can be made by examination of stained marrow cells through the microscope. Often, immunophenotyping or use of specially stained marrow cells is required to be sure of the distinction.

Blood Cell Count. A laboratory test requiring a small blood sample which can be used to measure the number and types of cells circulating in the blood. The term "complete blood count" or "CBC" is often used to refer to this test.

Blood Cells. Any of the three main types of cells in the blood: red cells, which carry oxygen; white cells, which principally prevent or combat infections; and platelets, which help prevent bleeding. There are several types of white cells in the blood. Each cell type is represented in blood in the numbers that meet the functions it serves. One fluid ounce of blood contains about 150 billion red cells, 8 billion platelets, and 20 million white cells. Red cells live for months, platelets live for a week or two, and white cells live for a few days. The marrow must replace over 500 billion cells from the blood each day.

Blood Plasma. See Plasma.

Bone Marrow. A spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation. By puberty, the marrow in the spine, ribs, breastbone,

hips, shoulders and skull is most active in blood cell formation. In adults, the bones of the hands, feet, legs and arms do not contain blood-forming marrow. In these sites the marrow is filled with fat cells. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried throughout the body.

Bone Marrow Aspiration. A test to examine marrow cells to detect cell abnormalities. A marrow sample is usually taken from the patient's hip bone. After medication is given to numb the area, the liquid sample is removed using a special needle inserted through the bone and into the bone marrow. The sample is looked at under a microscope for abnormal cells. The cells obtained can also be used for cytogenetic analysis and other tests.

Bone Marrow Biopsy. A test to examine marrow cells to detect cell abnormalities. This test differs from a bone marrow aspiration in that a small amount of bone filled with marrow is removed, usually from the hip bone. After medication is given to numb the area, a special biopsy needle is used to remove a core of bone containing marrow. The marrow is examined under a microscope to determine if abnormal cells are present. Bone marrow aspiration and biopsy may be done in the doctor's office or in a hospital. The two tests are almost always done together. Both tests are also done after treatment to determine the proportion of blood cancer cells that have been killed by therapy.

CBC. See Blood Cell Count.

Central Line. A special tube inserted into a large vein in the upper chest. The central line, sometimes referred to as an "indwelling 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, fluids or blood products or to withdraw blood samples. With meticulous care, central lines 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 be used for outpatient chemotherapy or blood product administration. Several types of catheters (for example, Groshong®, Hickman®, and Broviac®) can be used for patients receiving intensive chemotherapy or nutritional support.

Central Nervous System (CNS) Prophylaxis. Postremission treatment in which chemotherapy is placed in the fluid that bathes the spinal cord and brain. In certain types of leukemia, particularly acute lymphocytic (lymphoblastic) leukemia and acute monocytic leukemia with high blood cell counts, the leukemic cells have a propensity to enter the covering of the spinal cord and brain (the meninges). This process is often not apparent until months or years after remission when the leukemia returns, first in the coverings of the CNS, then in the marrow and blood. To prevent this type of relapse (meningeal leukemia), virtually all children and adults with acute lymphocytic leukemia who enter remission are treated with CNS

prophylaxis. In some cases, x-ray therapy is administered to the head as well. These approaches are very effective in eliminating leukemia cells in the meninges.

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 cancer 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 such as nausea, mouth sores and hair loss.

Chloroma. A solid tumor composed of immature granulocytes, including blast cells. Chloromas tend to occur in the brain or spinal cord and the bones, skin, or soft tissue of the head and neck, although they can develop anywhere in the body. They are usually treated with radiation or chemotherapy. Chloromas are an uncommon complication of AML. Other terms for chloroma are "granulocytic sarcoma" and "extramedullary myeloblastoma."

Chromosome. Any of the 46 structures in the nucleus of all cells in the human body (except the red blood cells) that contain a strand of DNA. This strand is made up principally of genes, which are specific stretches of the DNA. "Genome" is the term for an organism's complete set of DNA. The human genome has been estimated to contain about 30,000 genes. The genes on the X and Y chromosomes are the determinants of our gender: two X chromosomes produce a female and an X and a Y chromosome produce a male. Each chromosome has a long arm (called "q") and a short arm (called "p"). The number or size of chromosomes may be altered in blood cancer cells as a result of chromosome breakage and rearrangement. See Inversion; Translocation.

Clinical Trials. Carefully planned and monitored research studies, conducted by doctors. The goal of clinical trials for blood cancers is to improve treatment and quality of life and to increase survival. A treatment that is proven safe and effective in a clinical trial is often approved by the United States Food and Drug Administration (FDA) for use as a standard treatment if it is more effective or has fewer side effects than the current standard treatment.

Clonal. The designation for a population of cells derived from a single transformed parent cell. Virtually all cancers are derived from a single cell with an injury (mutation) to its DNA and thus are monoclonal. Leukemia, lymphoma, and myeloma are examples of clonal cancers; that is, cancers derived from a single abnormal cell.

Cluster Designation (CD). A term used with a number to identify a specific molecule on the surface of an immune cell. It is commonly used in its abbreviated form; for example, CD20 (the target of the monoclonal antibody therapy rituximab) and CD52 (the target of the monoclonal antibody therapy alemtuzumab).

Colony-Stimulating Factor. See Growth Factor.

Complete Blood Count. See Blood Cell Count.

Conditioning Treatment. Intensive therapy of a patient with cytotoxic drugs or drugs and total body radiation just before receiving a stem cell transplant. The therapy serves three purposes. First, it severely depresses the lymphocytes that are the key cells in the recipient's immune system. This action helps prevent the rejection of the graft (donor tissue). Second, it markedly decreases the number of marrow cells, which may be important to open up the special niches where the transplanted stem cells must lodge to engraft (survive). Third, if the patient is being transplanted for a malignancy, this intensive therapy greatly decreases the numbers of any remaining tumor cells.

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 given by matched or nearly matched unrelated donors.

Cycle of Treatment. An intensive, clustered period of chemotherapy and/or radiation therapy. The therapy may be given for several days or weeks, and this time period represents one cycle of treatment. The treatment plan may call for two, three or more cycles of treatment.

Cytogenetic Analysis. The process of analyzing the number and size of the chromosomes of cells. In addition to detecting chromosome alterations, in some cases it is possible to identify the actual genes that have been affected. These findings are very helpful in diagnosing specific types of blood cancers, in determining treatment approaches and in following the response to treatment. The individual who prepares and examines the chromosomes and interprets the results is called a "cytogeneticist."

Cytopenia. A reduction in the number of cells circulating in the blood.

Cytotoxic Drugs. Anticancer drugs that act by killing cells or preventing them from dividing. See Chemotherapy.

Deletion. A chromosomal abnormality in which part or all of a single chromosome has been lost.

Differentiation. The process by which stem cells give rise to functional cells of a single blood cell line. Differentiation of stem cells forms red cells, platelets and white cells (neutrophils, monocytes, eosinophils, basophils and lymphocytes).

DNA. The abbreviation for deoxyribonucleic acid, the genetic material in the cell. DNA is made up of a sugar-phosphate backbone with ladderlike "steps" composed of purines and pyrimidines (building blocks of nucleic acids). The sequence of the purines and pyrimidines in the DNA is responsible for passing genetic information to new cells during the process of cell division; for passing genetic information from one generation to the next during reproduction; and for providing the instructions for building proteins, which in turn carry out the major functions of a cell. A mutation is generally a change in or loss of the sequence of the purines or pyrimidines of the DNA. Mutations can lead to cell death, to changes in the way a cell functions or, in some cases, to cancer.

Donor Lymphocyte Infusion (DLI). A therapy that involves giving lymphocytes from the original stem cell donor to a patient who has had an allogeneic bone marrow transplant with a relapse of disease. DLI may induce an immune reaction against the patient's cancer cells. This therapy has been most effective in patients with chronic myeloid leukemia who relapse after transplantation but this therapy is being studied to treat patients with other blood cancers.

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

Epigenetic Change. Any change that alters gene activity without changing the DNA sequence. Many types of epigenetic changes have been identified. While epigenetic changes are natural and essential to many of the body's functions, certain epigenetic changes can cause major adverse health effects, including cancer. Drugs that target specific epigenetic changes—for example, the histone deacetylase (HDAC) inhibitor vorinostat (Zolinza®)—are approved to treat some blood cancers and are being studied in clinical trials for treatment of other blood cancers.

Erythrocytes. See Red Cells.

Erythrocyte Sedimentation Rate (ESR). See Sedimentation Rate.

Erythropoietin (EPO). A hormone required for the normal production of red blood cells. It is produced mainly by the kidneys and is released into the blood in response to decreased levels of oxygen in the blood. Epoetin alfa (Procrit® or Epogen®) and darbepoetin alfa (Aranesp®) are laboratory-made forms of the human hormone erythropoietin that can be used to treat anemia. In oncology, these drugs are used to assist in the recovery from chemotherapy-induced anemia or to treat chronic diseases in which anemia is a troublesome finding, such as lower-risk myelodysplastic syndromes. These drugs stimulate red cell production by the same mechanism as EPO; that is, by interacting with the EPO receptor on red cell progenitors.

ESR. See Sedimentation Rate.

Extramedullary Myeloblastoma. See Chloroma.

Farnesyl Transferase Inhibitor (FTI). A drug that has the potential to kill cancer cells by inhibiting or reversing the effect of farnesyl transferase, an enzyme needed to activate oncogenes (cancer-causing genes). FTIs, including tipifarnib (Zarnestra®) and lonafarnib (Sarasar®), are being studied to treat some blood cancers.

FDA. The short name for the United States Food and Drug Administration. Part of the FDA's job is to assure the safety and security of drugs, medical devices and the US food supply.

FISH. See Fluorescent In Situ Hybridization.

Flow Cytometry. A test that permits the identification of specific cell types within a sample of cells. 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. One use of flow cytometry is to determine whether a sample of cells is composed of T cells or B cells. This permits the physician to determine if the leukemia or lymphoma is of the B- or T-cell type. Flow cytometry is also used to select stem cells from a mixed-cell population so that they can be used later in a stem cell transplant.

FLT3. An abbreviation for the *Fms-like tyrosine kinase 3* gene. *FLT3* is expressed on blood-forming stem cells and plays a role in cell development. *FLT3* mutations can be detected in about one-third of AML patients. These mutations have been identified as part of the AML disease process and may become the basis for new targeted therapies.

Fluorescent In Situ Hybridization (FISH). A technique in which DNA probes tagged with fluorescent molecules that emit light of different wavelengths (and different colors) are used on tissue. The probes match to the chromosomes within the cells, and the chromosomes fluoresce in color. FISH is a means of studying chromosomes in tissue.

Fungus. A microbe often referred to as a "mold" or "yeast." There are many species of fungi, and some, while relatively harmless in people with healthy immune systems, are prone to produce serious infections in people who are immunosuppressed, as after stem cell transplantation or multiple treatments with high-dose chemotherapy for progressive leukemia or lymphoma. Fungi belong to the genera Candida, Aspergillus and Histoplasma, among others.

G-CSF (Granulocyte Colony-Stimulating Factor). See Growth Factor.

GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor). See Growth Factor.

Graft-Versus-Host Disease (GVHD). 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 donor T lymphocytes, which are present in the donor's blood or marrow, the source of the stem cells. The principal sites of injury 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. These reactions are mediated in part by antigens that are not in the major HLA system and cannot be matched prior to transplantation. For example, in the case of a female stem cell donor and a male recipient, factors that are produced by genes on the male recipient's Y chromosome may be seen as foreign by the female donor's cells, which do not share the genes on the Y chromosome. This fact does not prohibit female donors and male recipients, but it makes the risk of immune reaction higher.

Graft-Versus-Tumor Effect (Graft-Versus-Leukemia Effect). The potential immune reaction of transplanted (donor) T lymphocytes to recognize and attack the malignant cells of the recipient. This effect was noted when 1) disease recurrence after transplant was seen to be more likely if the donor and recipient were identical twins than if they were nonidentical siblings; 2) disease recurrence was less likely the more pronounced the graft-versus-host disease (GVHD) was; and 3) 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 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 types of myeloid leukemia, although it may also occur in patients with other blood cancers.

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. See Chloroma.

Growth Factor. A chemical used to stimulate the production of neutrophils and shorten the period of low neutrophil counts in the blood after chemotherapy. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are examples of growth factors that are made commercially. GM-CSF can also stimulate monocytes.

Hematocrit. The proportion of the blood occupied by the red cells. Normal values are 40 to 54 percent in males and 35 to 47 percent in females. If the hematocrit is below normal, the condition is called "anemia." If the hematocrit is above normal, the condition is called "erythrocytosis."

Hematologist. A medical doctor who specializes in the treatment of blood cell diseases. This person is either an internist who treats adults or a pediatrician who treats children.

Hematopathologist. A type of pathologist who studies diseases of blood cells by looking at peripheral blood smears, bone marrow aspirates and biopsies, and lymph nodes and other tissues. The hematopathologist uses his or her expertise to identify diseases such as blood cancers. In addition to using a microscope, a hematopathologist also uses laboratory values, flow cytometry and molecular diagnostic tests to make the most accurate diagnosis. The hematopathologist works closely with the hematologist/oncologist who sees the patient and decides on the best treatment based upon the 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 such as red cells or white cells of various types. This process is called "differentiation." The young or immature blood cells then further develop into fully functional blood cells. This process is called "maturation." The mature cells leave the marrow, enter the blood and circulate throughout the body. Hematopoiesis is a continuous process that is active normally throughout life. The reason for this activity is that most blood cells live for short periods and must be continually replaced. Red cells live for months, platelets live for a week or two, and white cells live for a few days. About 500 billion blood cells are made each day. When the marrow is invaded with cancer cells, it cannot produce enough normal blood cells to meet the constant demand for them, and the numbers in the blood cell counts become severely depleted.

Hemoglobin. The iron-containing pigment in red cells that carries oxygen to the tissue cells. A reduction in the number of red cells decreases the amount of hemoglobin in the blood. A decreased blood hemoglobin concentration is called "anemia." A low hemoglobin concentration decreases the oxygen-carrying capacity of blood. If severe, this decreased capacity may limit a person's ability to exert himself or herself. Normal values of blood hemoglobin are 12 to 16 grams per deciliter (g/dL). Compared to men, healthy women have, on average, about 10 percent less hemoglobin in their blood.

HLA. The abbreviation for human leukocyte antigen(s). These are proteins on the surface of most tissue cells, and they 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 factors is referred to as "tissue typing." There are six major groups of HLA: 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 (as in identical twins) or very similar (as in HLA-matched siblings), 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 (a result called "graft-versus-host disease").

Immune System. Cells and proteins that defend the body against infection. Lymphocytes, lymph nodes and the spleen are parts of the body's immune system.

Immunity. The ability to resist infection.

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 an antibody so that it can be detected. The tag can be identified by the laboratory detector used for the test. As cells carrying their array of antigens are tagged with specific antibodies, they can be identified; for example, myeloid leukemic cells can be distinguished from lymphocytic leukemic cells. Normal lymphocytes may be distinguished from leukemic lymphocytes. This method also helps subclassify cell types, information that may, in turn, help in deciding on the best treatment to apply in that type of leukemia or lymphoma. The antigen on a cell is referred to as a "cluster designation" or "CD," with an associated number. For example, CD10, also referred to as "CALLA" (common acute lymphoblastic leukemia antigen), may be present on leukemic lymphoblasts, and CD33, may be present on leukemic myeloblasts.

Immunosuppression. A state in which the immune system does not function properly and its protective functions are inadequate. The patient is more susceptible to infections, including those from microbes that are usually not highly infectious. This can occur as a result of intensive chemotherapy and radiation therapy, especially when used in high doses to condition a patient for transplantation. It can also occur because of disease states. Human immunodeficiency virus (HIV) infection is one such disease. Graft-versus-host disease (GVHD) creates an immunosuppressive state in which immune protection against infection is inadequate. In the transplant patient the conditioning regimen and severe GVHD can result in overwhelming infection. See Graft-Versus-Host Disease.

Immunotoxins. See Monoclonal Antibody Therapy.

Indwelling Catheter. See Central Line.

Intrathecal. The designation for the space between the covering or lining of the central nervous system (CNS) and the brain or spinal cord. This lining is called the "meninges." In some situations, drugs have to be administered directly into the spinal canal when leukemia cells are in the meninges. This is called "intrathecal therapy."

Inversion. An abnormality of chromosomes that occurs when a section of a chromosome breaks and turns upside down, so that its genetic material is in reverse order but the inverted piece remains attached to the chromosome.

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

Leukocytes. 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 in the concentration of blood leukocytes (white cells).

Lumbar Puncture. A procedure to remove spinal fluid from the space surrounding the spinal cord or to administer anticancer drugs to prevent or treat leukemia or lymphoma of the coverings of the central nervous system (CNS). The doctor first injects a local anesthetic, then inserts a needle between two vertebrae in the lower part of the back. Fluid samples are collected in sterile tubes and examined for evidence of leukemia or lymphoma. A lumbar puncture is not often used to test for AML, but may be used if the patient is having symptoms that could be caused by the spread of leukemia cells into the CNS. Another term for lumbar puncture is "spinal tap."

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 their location and the degree of enlargement.

Lymphocyte. A type of white cell that is the essential cell type in 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, which can attack virus-infected cells or tumor cells.

Macrophage. See Monocyte.

Marrow. See Bone Marrow.

Microliter (µL) of Blood. A measurement used for some blood test results. One microliter (µL) is an amount equal to one one-millionth of a liter, which is almost equal to a quart of blood.

Minimal Residual Disease (MRD). The small amounts of cancer cells that may remain after treatment, even when blood and marrow may appear to be normal. These residual cells can only be identified by sensitive molecular techniques.

Monoclonal. See Clonal.

Monoclonal Antibodies. Antibodies made by cells belonging to a single clone. These highly specific antibodies can be produced in the laboratory. They are very important reagents for identifying and classifying disease by the immunophenotyping of cells. They also have clinical applications for targeted delivery of drugs to cancer cells and can be used to purify cells used for stem cell transplants.

Monoclonal Antibody Therapy. Therapy using proteins made in the laboratory that either react with or attach to antigens on the cancer cells to which they are targeted. The antibodies are used therapeutically in three ways: as "naked" antibodies (monoclonal antibodies); as antibodies to which radioactive isotopes are attached (radioimmunotherapies); and as antibodies to which toxins are attached (immunotoxins).

Monocyte/Macrophage. A type of white cell that represents about 5 to 10 percent of the cells in normal human blood. The monocyte and the neutrophil are the two major microbe-eating and microbe-killing cells in the blood. 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 (in this function it is called a "scavenger cell") and assist lymphocytes in their immune functions.

Multidrug Resistance (MDR). A characteristic of cells that makes them resistant to the effects of several different classes of drugs. There are several forms of drug resistance. One type of MDR involves the ability to force several drugs out of the cell. The 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 a protein that prevents the drugs from affecting 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 part of the DNA that represents that 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 that tissue cell into a tumor. Most cancers start after a somatic mutation. In leukemia, lymphoma or myeloma, a primitive marrow (blood-forming) or lymph node cell undergoes one or more

somatic mutations, leading to the formation of a tumor. If the mutation results from a major abnormality of chromosomes, such as a translocation, it can be detected by cytogenetic examination. Sometimes the alteration in the gene is subtler and requires more sensitive tests to identify the oncogene.

Myeloblasts. See Blast Cells.

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

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

Neutrophil. 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. Several subtypes of acute myeloid leukemia, acute lymphocytic leukemia and lymphoma, and nearly all cases of chronic myeloid leukemia are associated with an oncogene.

Oncologist. A medical doctor 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 doctors cooperate and collaborate to provide the best treatment plan (surgery, radiation therapy, chemotherapy or immunotherapy) for the patient.

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

Pathologist. A medical doctor who identifies disease by studying tissues under a microscope. See Hematopathologist.

Peripheral Blood Smear. A sample of blood placed on a slide and dyed so that the cells can be examined under a microscope.

Peripherally Inserted Central Catheter (PICC or PIC Line). A long, thin, flexible tube that is inserted into the body and used to administer medications, antibiotics, fluids and nutrition for an extended period of time. It can also be used to obtain blood samples. Prior to insertion of the PICC, the patient is given a local anesthetic to numb the arm between the elbow and the shoulder. The PICC is inserted through the skin into a vein in the arm and advanced until it reaches the superior vena cava just above the heart. The superior vena cava is one of the veins

in the central venous system. The PICC can be maintained for several weeks to months, eliminating the need for standard intravenous (IV) administration.

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 such as bacteria and fungi and kill them as a means of protecting the body against infection. The two principal phagocytes are neutrophils and monocytes. They leave the blood and enter tissues in which an infection has developed. A severe decrease in the concentration of these cells is the principal cause of susceptibility to infection in patients treated with intensive radiation therapy and/or chemotherapy. Treatment may suppress blood cell production in the marrow, resulting in deficiencies of these phagocytic cells.

PIC/PICC Line. See Peripherally Inserted Central Catheter.

Plasma. The liquid portion of the blood, in which the blood cells, platelets, proteins and various other components are suspended. It is also referred to as "blood plasma."

Platelets. Small blood cells (about one-tenth the volume of red cells) that stick to the site of blood vessel injury, aggregate and then 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 (too few) or thrombocythemia (too many).

Platelet Transfusion. Transfusion of donor platelets, which may be needed to support some patients treated for blood cancer. The platelets can be gathered from several unrelated donors and given as pooled, random-donor platelets. The platelets from about six single-unit blood donors are required to significantly raise the platelet count in a recipient. Sufficient platelets can be obtained from one donor by a procedure known as "apheresis." This technique skims the platelets from large volumes of blood as it passes through the apheresis machine. The red cells and plasma are returned to the donor. The advantage of single-donor platelets is that the patient is not exposed to the different antigens on platelets from many different people and thus is less likely to develop antibodies against donor platelets. HLA-matched platelet transfusion can be given from a related donor who has an identical or very similar HLA tissue type.

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 determined or studied. This technique has become useful in detecting a very low concentration of residual blood cancer cells, too few to be seen using a microscope. PCR can detect the presence

of one blood cancer cell among 500,000 to 1 million blood cells. PCR requires a specific DNA (or RNA) abnormality or marker, like an oncogene, in the leukemia or lymphoma cells in order to be used for identifying residual abnormal cells.

Port. A small device that is used with a central line to access a vein. The port is placed under the skin of the chest. To take blood samples (or to give medicines or nutrition) the doctor or nurse puts a needle through the skin into the port. A numbing cream can be put on the skin before the port is used.

Promyelocyte. A cell of the marrow that is very early in development along the pathway to myeloid cells. It represents the next stage after the blast cell stage.

Radiation Therapy. The use of x-rays and other forms of radiation in treatment. Radiation therapy may be useful in the treatment of some localized blood cancers. Radiation therapy can be an important adjunct to therapy when there are particularly large masses in a localized area or when local large lymph nodes are compressing or invading normal organs or structures and chemotherapy cannot control the problem.

Radioimmunotherapies. See Monoclonal Antibody Therapy.

Recurrence/Relapse. The return of a disease after it has been in remission following treatment.

Red Cells. Blood cells (erythrocytes) that carry hemoglobin, which binds oxygen and carries it to the tissues of the body. The red cells make up about 40 to 45 percent of the volume of the blood in healthy individuals.

Reduced-Intensity Stem Cell Transplantation. A form of allogeneic transplantation, now in clinical trials. In a reduced-intensity transplant, patients receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. Immunosuppressive drugs are used to prevent rejection of the graft (donor tissue), and the engraftment of donor immune cells may allow these cells to attack the disease (graft-versus-leukemia effect). More study is needed to determine the effectiveness of this treatment for non-Hodgkin lymphoma patients. Studies to determine the usefulness of reduced-intensity stem cell transplantation in older patients are also under way. For more information about all types of stem cell transplantation, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Refractory Disease. Disease that does not go into remission or improve substantially after treatment with standard therapy for the disease. Newly diagnosed patients or relapsed patients may have refractory disease. See Resistance to Treatment.

Relapsed Disease. Disease that initially responded to therapy but has begun to progress.

Remission. The disappearance of evidence of a disease, usually as a result of treatment. The terms "complete" and "partial" are sometimes used to modify the term "remission." Complete remission means that all evidence of the disease is gone. Partial remission means that the disease is markedly improved by treatment, but residual evidence of the disease is present. 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. Refractory leukemia is the condition in which a proportion of malignant cells resists the damaging effects of a drug or drugs. Cells have several ways to develop drug resistance. See Multidrug Resistance.

Risk Factor. A factor that is scientifically established to increase a person's chance of getting a disease. Risk factors can be classified as either genetic (inherited), lifestyle related, or environmental. The presence of one or more risk factors does not mean that a person will necessarily develop the disease. In the case of environmental exposure, the extent of exposure and its duration are important considerations in determining if risk is increased.

RNA. Abbreviation for ribonucleic acid, a molecule in cells that carries out DNA's instructions for making proteins.

Sedimentation Rate. A blood test that measures how quickly red cells (erythrocytes) settle in a test tube in 1 hour. A sedimentation rate test is done to find out if inflammation is present in the body, to check on the progress of a disease or to see how well a treatment is working. This test is also called a "sed rate" or "erythrocyte sedimentation rate (ESR)."

Serum. The liquid portion of the blood in which no cells are present.

Somatic Cell Mutation. See Mutation.

Spinal Tap. See Lumbar Puncture.

Spleen. An organ located in the left upper portion of the abdomen just under the left side of the diaphragm. It contains clusters of lymphocytes and also filters old or worn-out cells from the blood. It is often affected in lymphocytic leukemia and lymphoma. Enlargement of the spleen is called "splenomegaly." Surgical removal of the spleen is known as "splenectomy." Certain diseases are treated by removing the spleen. Most of the functions of the spleen can be performed by other organs, such as the lymph nodes and liver, but a person whose spleen has been removed is at higher risk for infection. He or she is given antibiotic therapy immediately at the first sign of infection, such as a fever.

Stem Cells. Primitive cells in marrow that develop into red cells, white cells and platelets. 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 the blood can be collected, preserved by freezing and later thawed and used for stem cell therapy. See Hematopoiesis.

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

Thrombocythemia. An above-normal concentration of platelets in the blood.

Thrombocytopenia. A below-normal concentration of platelets in the blood.

Toxin. A naturally derived substance that is poisonous to cells. A toxin can be attached to antibodies that then attach to cancer cells. The toxin may kill the cancer cells.

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 occurs, the gene at which the break occurs is altered. This is one form of somatic mutation that may transform the gene into an oncogene (cancer-causing gene). See Mutation.

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

Tumor Suppressor Gene. A gene that acts to prevent cell growth. If a mutation occurs in this gene that "turns off" the gene and causes loss of function, it may make the individual more susceptible to the development of cancer in the tissue in which the mutation occurred. Another term for tumor suppressor gene is "antioncogene."

White Cells. Any of the five major types of infection-fighting cells in the blood: neutrophils, eosinophils, basophils, monocytes and lymphocytes. White cells are also called "leukocytes."

More Information

Free LLS publications include

Blood Transfusion
Cancer-Related Fatigue Facts
Choosing a Blood Cancer Specialist or Treatment Center
The AML Guide—Information for Patients and Caregivers
Understanding Clinical Trials for Blood Cancers
Understanding Drug Therapy and Managing Side Effects
Understanding Lab and Imaging Tests

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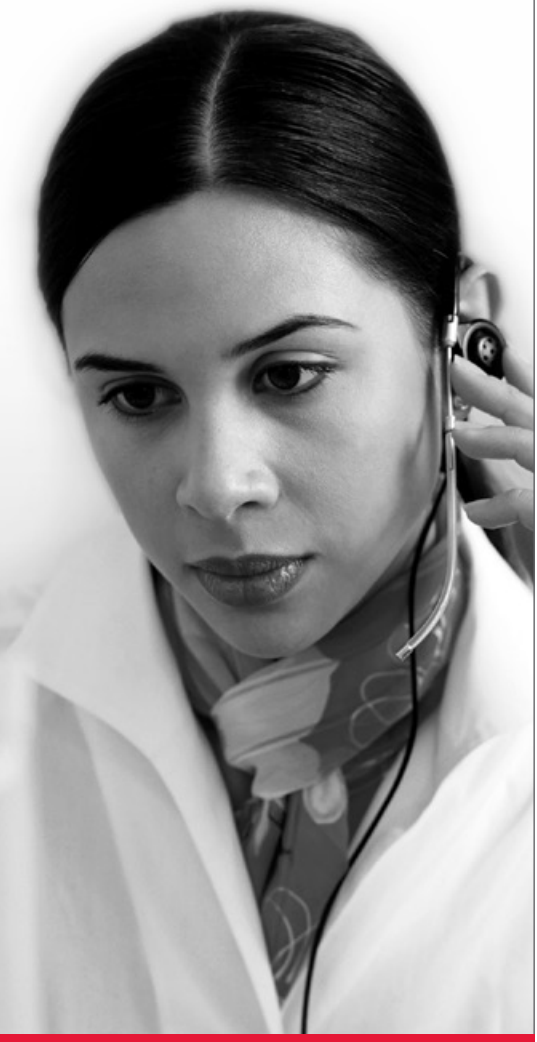

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