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LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Acute Lymphoblastic Leukemia

Danielle, ALL survivor

This publication was sponsored by AMGEN Jazz Pharmaceuticals

Revised **2014**

A Message From Louis J. DeGennaro, Ph.D.

Interim President and CEO of The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society (LLS) believes we are living at an extraordinary moment. 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. An important part of our mission is bringing you the latest information about advances in treatment for acute lymphoblastic leukemia (ALL), so you can work with your healthcare team to determine the best options for the best outcomes. Our vision is that one day the great majority of people who have been diagnosed with ALL 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 1954, LLS has been a driving force behind almost every treatment breakthrough for patients with blood cancers, and we have awarded almost $1 billion to fund blood cancer research. Our commitment to pioneering science has contributed to an unprecedented rise in survival rates for people with many different blood cancers. Until there is a cure, LLS will continue to invest in research, patient support programs and services that improve the quality of life for patients and families.

We wish you well.

Louis J. DeGennaro, Ph.D.
Interim President and CEO

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Acknowledgement

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Introduction

This booklet provides information about acute lymphoblastic leukemia (ALL) for patients and their families. Brief descriptions of normal blood and marrow, the lymphatic system and definitions of medical terms are included.

ALL may be called by other names, including "acute lymphocytic leukemia" and "acute lymphoid leukemia."

About 6,070 new cases of ALL were expected to be diagnosed in the United States in 2013. Based on the most current data, an estimated 66,030 people are living with, or are in remission from, ALL. Although ALL can occur at any age, it is the most common type of leukemia in children and young adults younger than 20 years.[1]

Advances in the treatment of ALL have resulted in improved remission rates. The number of patients who have gone into remission or have been cured is increasing. New therapies are under study in clinical trials.

[1] Source: Surveillance, Epidemiology and End Results (SEER) Program (www.seer.cancer.gov). National Cancer Institute, DCCPS, Surveillance Research Program, Statistical Research and Applications Branch, updated April, 2013.

Here to Help

This booklet will be helpful when you talk to your doctor about your diagnosis and 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 ALL 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 their treatment plan is established and they can look forward to recovery.
- The outlook for people with ALL 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 ALL will affect your daily life, at least for a time. During and after treatment, you may want to have friends, family members

or caregivers help you get information and support. 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.

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

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 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.

Advocacy and Public Policy. The LLS Office of Public Policy (OPP) enlists volunteers to help advocate for policies and laws to speed the development of new treatments and improve access to quality medical care. Visit www.LLS.org/advocacy to find out more or get involved.

Co-Pay Assistance Program. This program offers assistance for financially eligible patients with certain blood cancer diagnoses to help pay for private or public health insurance premiums and/or co-pay costs for prescription medications. Check www.LLS.org/copay or call (877) 557-2672 to speak to a Co-Pay Assistance Program specialist for eligibility information.

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.

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.

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 chapter by calling (800) 955-4572 or by visiting www.LLS.org/chapterfind.

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.

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, please visit www.LLS.org/programs.

Children's Concerns. Each family that receives a diagnosis of childhood ALL is thrown into an unfamiliar world of treatment and follow-up care. The child, parents and siblings need support. Remember that help is available. Don't hesitate to ask for assistance for your child, yourself or other family members, even if you are already working with a psychologist, social worker or child life specialist. For practical guidance on how to support your child and other family members, deal with your own concerns, share the news with extended family and friends and make the transition to life after treatment ends, see the free LLS publication *Coping With Childhood Leukemia and Lymphoma*.

The Trish Greene Back to School Program for Children With Cancer. This program is designed to increase communication among healthcare professionals, school personnel, parents and patients to assure children with cancer a smooth transition back to school. For more information about these and other programs, contact your LLS chapter by visiting www.LLS.org/chapterfind.

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 ALL.
- 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.

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.

Information for World Trade Center Survivors. People who were involved in the aftermath of the attacks of September 11, 2001, may be eligible for help from the World Trade Center Health Program. These include: responders, workers and volunteers who helped with rescue, recovery and cleanup at the World Trade Center and related sites in New York City; survivors who were in the New York City disaster area, lived, worked, or were in school in the area; and responders to the Pentagon and the Shanksville, PA crash who have been diagnosed with a blood cancer. For more information, call the World Trade Center Health Program at (888) 982-4748 or visit www.cdc.gov/wtc/faq.html.

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 treatment. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a two-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 leukemia is a rapidly progressing disease that produces cells that are not fully developed. These cells cannot carry out their normal functions. Chronic leukemia usually progresses slowly and patients have greater numbers of mature cells. In general, these more mature cells can carry out some of their normal functions (see *Normal Blood and Marrow* on page 31).

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

The four main types of leukemia are further classified into subtypes. Knowing the subtype of your disease is important because your treatment plan is based in part on the subtype (see *ALL Subtypes* on page 10).

More general information about leukemia is given in the free LLS publications *Understanding Leukemia* and *The ALL Guide–Information for Patients and Caregivers*.

Acute Lymphoblastic Leukemia

How ALL Develops. ALL results from an acquired or a genetic injury to the DNA of a single cell in the marrow. The effects of ALL include uncontrolled and exaggerated growth and accumulation of cells called "lymphoblasts" or "leukemic blasts," which fail to function as normal blood cells.

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

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

Incidence, Causes and Risk Factors. ALL occurs most often in the first decade of life but increases in frequency again in older individuals (see Figure 1, below).

Acute Lymphoblastic Leukemia: Age-Specific Incidence Rates (2006-2010)

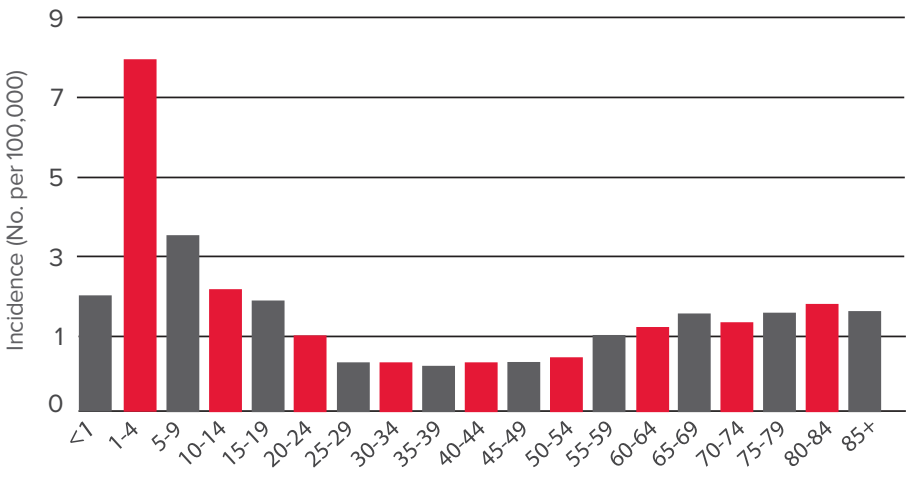

Figure 1. | The horizontal axis shows five-year age intervals. The vertical axis shows the frequency of new cases of ALL per 100,000 people, by age-group. Note that the risk of ALL is greatest in the first five years of life. An increase in occurrence is also seen in older individuals (source: Surveillance, Epidemiology and End Results [SEER] Program; National Cancer Institute; 2013)

The causes of ALL are not clear. A few factors have been associated with an increased risk of developing the disease. Exposure to high doses of radiation (carefully studied in the survivors of atomic bomb detonations in Japan) is one such factor. ALL occurs at different rates in various settings. There are higher leukemia rates in more developed countries and in higher socioeconomic groups. These and other findings have led to a hypothesis that reducing children's exposure to bacterial infections during the first year of life may have increased the risk of childhood ALL. Nonetheless, there have been other life-saving benefits from avoidance of bacterial infections during infancy. A child who has had multiple diagnostic x-rays may be at a slightly increased risk for ALL; however, more studies need to be done to confirm these research findings. Previous chemotherapy and radiation treatment may be a cause of ALL in adults.

Scientists continue to explore possible relationships to lifestyle or environmental factors. Research supports the view that a number of complex factors may be involved. One study found that children exposed to agricultural pesticides applied near their home may experience a significant increased risk of ALL. The findings from other studies have not been definitive, which is confusing for patients and their families. They may wonder what they could have done differently to avoid the disease; unfortunately, at the present time, there is no answer to that question.

Some cases of ALL relate to a mutation in a lymphocyte that occurs during the prenatal period (in utero). Usually the leukemia is diagnosed in infancy or in the first few years after birth. However, in some cases, years may pass before the disease appears. With ALL, it seems that additional genetic abnormalities can occur after birth and allow the unregulated cell growth that is needed to trigger the disease, because there are more mutations found in utero than there are cases of childhood ALL.

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

To begin determining the reason for these signs and symptoms, your doctor will want to examine your blood by doing a blood test called a complete blood count (CBC). Low numbers of red blood cells, white blood cells and platelets are common in patients with newly diagnosed ALL.

Other signs and symptoms that a person with ALL may have include

- Pale skin coloring 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
- Frequent minor infections
- Discomfort in bones or joints
- Enlarged spleen, liver or lymph nodes.

Leukemic cells can also collect in the testes in a small number of patients.

Bleeding. A low platelet count predisposes patients to bleeding. Bleeding in the brain or lung is serious and can be fatal. However, such bleeding usually comes after minor bleeding, such as nosebleeds, blood in the urine or bruises (see *Low Blood Cell Counts* on page 24).

Infection. Severe infection usually does not occur at the time of diagnosis. If the neutrophil count becomes or remains low because of ALL or its treatment, serious infection may occur and can be life threatening. However, if proper precautions are taken during therapy, most patients do not develop life threatening infections (see *Infection* on page 25).

A person who has signs or symptoms that suggest the possibility of leukemia is usually referred to a specialist. This may be a hematologist/oncologist. The specialist will order additional tests to make a diagnosis. The signs and symptoms of ALL are also seen in a number of other, less serious diseases.

Diagnosis and Cell Classification

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.

Blood and Bone Marrow Tests. Blood and bone marrow cells are examined to diagnose ALL and identify the ALL subtype (see *ALL Subtypes* on page 10). An examination of the stained (dyed) blood cells with a light microscope will often show the presence of leukemic blast cells (immature cells that do not function like normal, mature white blood cells). A bone marrow examination is preferred to diagnose ALL because a proportion of patients do not have leukemic blasts circulating in the blood at the time of diagnosis (see Figure 2, below).

ALL Blast Cells

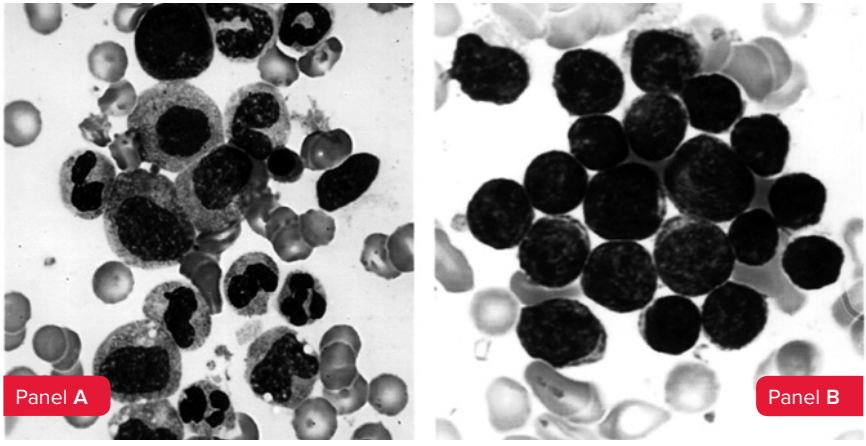

Figure 2. | **Panel A** shows a photograph of developing cells in healthy marrow. The variation in the appearance of the cells is characteristic of normal marrow. **Panel B** shows a photograph of marrow cells from a patient with acute lymphoblastic leukemia. An unvaried appearance characterizes the leukemic blast cells.

Blood and Marrow Samples. To do the blood 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 bone marrow biopsy (see page 36). The cells from the blood and marrow samples are examined under a microscope. Your doctor will work with a hematopathologist, a specialist who studies blood diseases by looking at the samples of blood and marrow cells and other tissues.

ALL Subtypes. ALL has many subtypes and can be classified by immunologic, cytogenetic and molecular genetic tests. Some of these tests may be repeated during and after therapy to measure the effects of treatment. Depending on the subtype, the doctor will determine which drugs or drug combinations, drug dosages, and duration of treatment are most appropriate for the patient, and whether other types of treatment, such as stem cell transplant, are needed to achieve the best results.

Immunophenotyping, a process used to identify cells based on the types of proteins (antigens) on the cell surface, is necessary to establish the diagnosis of either B-cell ALL, T-cell ALL or acute myeloid leukemia (AML). "Flow cytometry" is the name of one test that may be used to do immunophenotyping.

ALL is divided into two major subtypes based on the physical characteristics and the level of development of the leukemia cells. This basic classification helps the treatment team to start planning the best course of treatment for the patient. The principal ALL subtypes are

- B lymphoblastic leukemia
- T lymphoblastic leukemia

The phenotype or physical characteristics of the leukemia cell determine whether the cells are of B-cell or T-cell origin. The B-cell subtype is identified by finding cell surface markers on the leukemic blast cells that are the same as those that develop on normal B lymphocytes. The T-cell subtype is identified by finding cell surface markers on the leukemic blast cells that are the same as the ones that develop in normal T lymphocytes.

Not all B lineage disease is treated the same. Mature B-cell leukemia is also known as "Burkitt leukemia/lymphoma." It accounts for 2%-3% of ALL patients. The treatment for Burkitt leukemia is based on therapy for non-Hodgkin lymphoma and is completely different than the treatment used for ALL. For more information, see the free LLS publication *Non-Hodgkin Lymphoma*.

In some studies, ALL has been subdivided into CD10 (the common acute lymphoblastic leukemia antigen, abbreviated cALLa) positive and CD10 negative. However, these categories of ALL have not been used in determining treatment approach.

Genetic classification of ALL cells is also important (See Table 1 on page 12). About 75 percent of adult and childhood cases can be classified into subgroups based on the chromosome number or DNA analysis, specific chromosomal rearrangements and molecular genetic changes.

"Karyotyping" and "cytogenetic analysis" are processes used to identify certain changes in chromosomes and genes. Laboratory tests called "fluorescence in situ hybridization (FISH)" and "polymerase chain reaction (PCR) assays" may be done, in which cells in a sample of marrow are studied to look for certain changes in the structure or function of genes. In some cases, other special tests may be used. See the free LLS publication *Understanding Lab and Imaging Tests* for more comprehensive information about these tests.

Examination of leukemic cells by cytogenetic techniques permits identification of chromosome or gene abnormalities. Translocations are the most common type of DNA change that is associated with ALL. In a translocation, the DNA from one chromosome breaks off and becomes attached to a different chromosome. Other chromosome changes such as deletions (part of the chromosome is lost) and inversions (rearrangement of the DNA within part of a chromosome) can also lead to the development of ALL, but these changes are less common. In many cases of ALL, the genetic changes are not known. Not all ALL cases exhibit the same chromosome changes. Some are more common than others and some have a greater effect on the patient's prognosis than others.

Other features that are important in guiding treatment approach include the age of the patient, level of the white blood cell count, involvement of the central nervous system and involvement of lymph nodes.

Table 1. ALL Principal Cytogenetic Abnormalities

Abnormality	Associated Prognosis
Hyperdiploidy More than the normal number of 46 chromosomes	Favorable prognosis
Hypodiploidy Fewer than the normal number of 46 chromosomes	Poor prognosis
Translocation between chromosomes 12 and 21	Favorable prognosis
"Philadelphia" or "Ph" chromosome Translocation between chromosome 22 and chromosome 9	Favorable prognosis with contemporary therapy
"Ph-like" ALL (*BCR-ABL1*-negative)	Poor prognosis
Translocation between chromosome 1 and 19 (associated with CNS leukemia)	Favorable prognosis with contemporary therapy
Translocation between chromosome 4 and 11 (associated with infant and older adult age-groups, CNS leukemia)	Poor prognosis
Translocation between chromosome 11 and 19	Poor prognosis for infants Better prognosis for older children
Translocation between chromosome 8 and 14	Favorable prognosis with short-term intensive therapy
***CRLF2* and Janus kinase gene mutations**	Poor prognosis
***NOTCH1* mutations**	Favorable prognosis
HOX11 overexpression	Favorable prognosis with chemotherapy alone
Chromosome 21 amplification	Requires intensive therapy to avert poor prognosis

Treatment

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

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

- The ALL subtype
- The type of leukemic lymphocytes as judged by their appearance
- Immunophenotype and chromosome composition
- Whether the patient has received chemotherapy in the past to treat another type of cancer
- Whether the ALL is present in the central nervous system or other sites outside of the bone marrow
- Whether the ALL has not responded to treatment or has relapsed
- The presence of systemic infection at diagnosis
- The patient's age and general health.

Fast Facts about Treatment Planning

- A person who has ALL is usually treated by a hematologist/oncologist.
- It is essential to seek treatment in a center where doctors are experienced in the care of patients with acute leukemia.
- Patients with ALL 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.

Fast Facts About Children and Adolescents

- For many children, ALL is curable with current therapies.
- A number of cancer centers are using pediatric protocols to treat adolescent and young adult patients.

Fast Facts About Treatment

- For older ALL patients, age alone is not a reason to withhold treatment.
- 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.
- In most patients, intensive chemotherapy is required to achieve complete remission. At least two drugs are combined to treat patients initially.
- The age of the patient and the type of leukemic lymphocytes based on their appearance, immunophenotype or chromosome composition can influence the type of treatment given.
- More treatment is needed once a remission is achieved to help prevent a relapse.
- Postremission treatment may consist of maintenance chemotherapy or stem cell transplantation.
- If relapse occurs, treatment options may include different chemotherapy regimens, allogeneic stem cell transplantation or other investigational therapies.
- 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.

Talk to your doctor about

- Your treatment options and the results you can expect from treatment
- The results you might expect with standard therapy
- The possibility of participating in a clinical trial

Pretreatment Considerations. Adults of childbearing age and parents of children diagnosed with ALL should ask the doctor for information about addressing the risk for infertility. See the free LLS publication *Fertility* for more details.

Chemotherapy. There are three parts to the treatment for ALL. These are induction, consolidation (also called "intensification") and maintenance. (see Figure 3 on page 19.) Consolidation and maintenance are postremission therapies.

Induction Therapy. The initial phase of chemotherapy is called "induction." The specific drugs, the dosages used, and the timing of their administration, depend on several factors, including the patient's age, the specific features of the leukemia and the overall health of the patient. Several drugs are combined. Typically, the severity of the disease and the side effects of this initial therapy result in an initial hospital stay of four to six 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.

A central line (indwelling catheter) 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 catheter (port) can be used to administer medications, fluids or blood products or to withdraw blood samples for cell counts and chemical tests. An alternative is a PICC line (percutaneously inserted central venous catheter), which can be placed in a vein of the upper arm. See the free LLS publication *Understanding Side Effects of Drug Therapy* for additional information about drug administration.

The goal of induction therapy is to achieve a remission, which means to rid the blood and marrow of visible leukemic blast cells. A remission is not a cure but it is a very important part of the process as it allows normal marrow cells to develop and the patient's blood counts return to normal levels. Generally, if blast cells are still evident after the first course of induction chemotherapy, a second course of chemotherapy, usually using different drugs is given. Table 2, on page 16, gives examples of the drugs that may be used for induction and postremission treatment as well as some of the drugs under study in ALL clinical trials. Other drugs may be added or substituted for higher-risk, refractory or relapsed patients. Allogeneic stem cell transplantation may be added to the treatment plan for patients with relapsed ALL or for patients at high risk of relapse after chemotherapy (see pages 21 through 23). Autologous stem cell transplantation is not commonly used to treat ALL because of the high relapse rate following this type of transplant.

A child with ALL is usually admitted to the hospital, as soon as the diagnosis is known, to start the induction treatment. Most children enter remission after the first month of therapy. For some children this is the first time they have stayed away from home for an extended period of time. Providing age-appropriate information to your child about the illness and treatment will help him or her to build trust in both you and the treatment team and to feel comfortable talking about fears and concerns. For practical guidance about how to support your child and other family members, deal with your own concerns, share the news with extended family and friends and make the transition to life after treatment ends, see the free LLS publication *Coping With Childhood Leukemia and Lymphoma*.

Table 2. Some Drugs Used for Treatment and/or in Clinical Trials for ALL

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

Antitumor Antibiotics

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

DNA-Repair Enzyme Inhibitors

- etoposide (VP-16; VePesid®, Etopophos®)
- teniposide (VM-26; Vumon®)
- topotecan (Hycamtin®)

DNA Synthesis Inhibitor

- carboplatin (Paraplatin®)

DNA-Damaging Agents

- cyclophosphamide (Cytoxan®)
- ifosfamide (Ifex®)

Enzymes That Prevent Cells From Surviving

- Asparaginase *Erwinia chrysanthemi* (Erwinaze®)
- pegaspargase (PEG-L-asparaginase; Oncaspar®)

Tyrosine Kinase Inhibitors

- imatinib mesylate (Gleevec®)
- dasatinib (Sprycel®)
- nilotinib (Tasigna®)
- ponatinib (Iclusig®)

Antimetabolites

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

Drug That Prevents Cells From Dividing

- vincristine (Oncovin®)
- liposomal vincristine (Marqibo®)

Synthetic Hormones

- prednisone
- prednisolone
- dexamethasone

Monoclonal Antibodies

- alemtuzumab (Campath®)
- rituximab (Rituxan®)

Table 2. | Lists some of the standard drugs and some of the drugs currently being studied to treat ALL patients. Various approaches to ALL 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. However, it is essential to seek treatment in a center where doctors are experienced in the care of patients with acute leukemia.

Table 3. Examples of Therapy Used in the Treatment of ALL

Induction therapy given in the first month may include

- Doxorubicin or daunorubicin by vein
- Asparaginase by injection into a muscle or by vein
- Vincristine by vein
- Corticosteroid (dexamethasone or prednisone) by mouth
- Methotrexate by injection into the spinal fluid
- 6-Mercaptopurine by mouth
- Cytarabine by injection into the spinal fluid.

Postremission therapy given in cycles for two to three years may include

- Vincristine by vein
- Cyclophosphamide by vein
- Daunorubicin or doxorubicin by vein
- Thioguanine by mouth
- Prednisone or dexamethasone by mouth
- Mercaptopurine by mouth
- Methotrexate by mouth, by vein, or into a muscle
- Methotrexate by injection into the spinal fluid
- Cytarabine by injection into the spinal fluid
- Hydrocortisone by injection into the spinal fluid
- Radiation therapy to the head.

Postremission Therapy (Consolidation and Maintenance Therapy). Since residual leukemia cells that are undetectable by blood or marrow examination remain after remission, the optimal treatment for patients who have ALL requires additional intensive postremission therapy. As in the induction phase, individual factors such as the age of the patient, the ability to tolerate intensive treatment, cytogenetic findings, the availability of a stem cell donor and other considerations may influence the treatment approach.

Consolidation therapy is usually given in cycles for four to six months. The goal of this phase of treatment is to reduce the number of leukemic cells still remaining. Generally, several chemotherapy drugs are combined to help prevent the leukemia cells from developing drug resistance. When necessary, intrathecal therapy (drugs that are administered directly into the spinal canal) is continued.

Maintenance therapy is usually given for about two years. During the first months of maintenance, treatment protocols may include one or two intensified treatments similar to the ones used during induction. These intensified treatments are also known as "re-induction" or "delayed intensification" treatments. In most cases, postremission chemotherapy also includes drugs not used during induction treatment (see Table 3 on page 17).

Some types of high-risk ALL—such as T-cell ALL or ALL in the very young (infants) or in adults—are usually treated with higher doses of drugs during induction, consolidation and maintenance therapy.

Central Nervous System (CNS) Prophylaxis. ALL cells often collect in the lining of the spinal cord and brain, called the "meninges." If not treated, the meninges can harbor leukemia cells, and relapse can occur in these sites (meningeal leukemia). For this reason, treatment called "central nervous system prophylaxis" is directed to those sites. The treatment involves injecting drugs, such as methotrexate, into the spinal column. Areas of the body that are less accessible to chemotherapy given by mouth or in the vein are sometimes referred to as "sanctuary sites." Cranial radiation for pediatric patients, except in cases of T-cell ALL and patients who have a CNS relapse, is not being used in some doctors' practices. Treatment without radiation decreases the chance of long-term and late effects for the patient, such as organ damage, the development of second cancers and neurocognitive impairment.

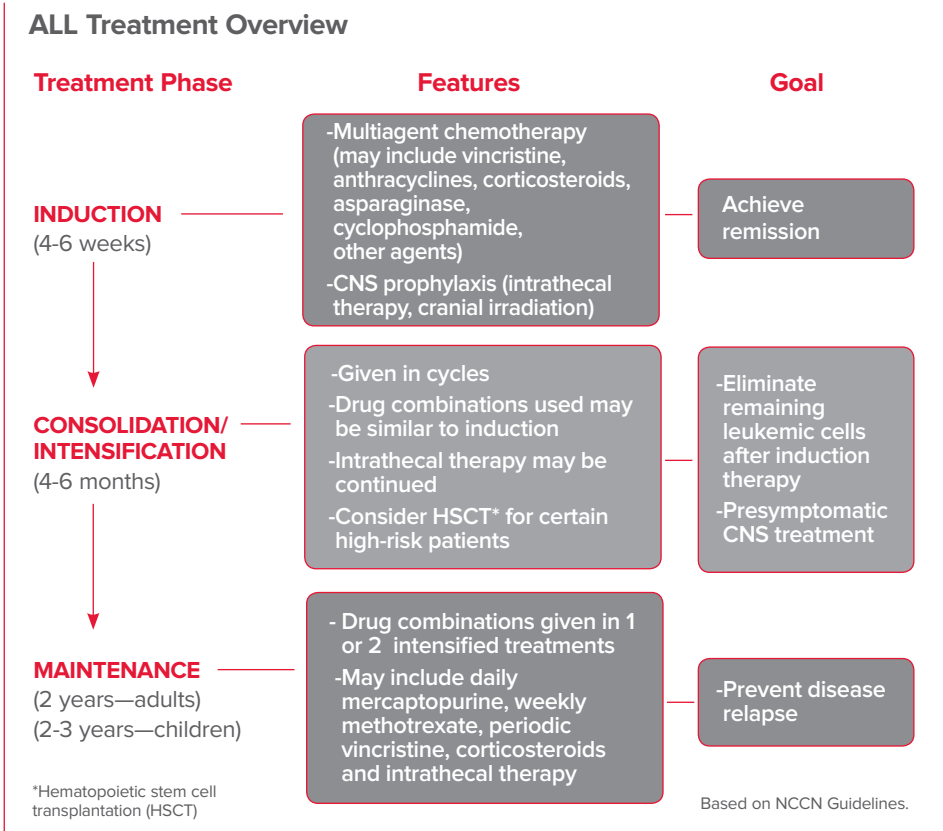

Figure 3. | The figure above provides general information. There are many different ALL treatment approaches. Speak to your doctor to develop a treatment plan specific to you.

Ph-Positive ALL. About one out of four to five adults with ALL and a small number of children (about 2 to 4 percent) with ALL have a subtype called "Ph-positive (Philadelphia-positive) ALL." Patients with this subtype of ALL have a chromosome alteration that results in a specific gene mutation referred to as "*BCR-ABL*." These patients are treated with the tyrosine kinase inhibitor drugs (TKIs) imatinib mesylate (Gleevec®), dasatinib (Sprycel®), nilotinib (Tasigna®) or ponatinib (Iculsig®), in addition to other multidrug chemotherapy. Gleevec treatment with chemotherapy is effective for some Ph-positive ALL patients. Sprycel and Tasigna are used to treat Ph-positive ALL patients who do not tolerate or respond to Gleevec or those who develop resistance to it. Iclusig is FDA approved to treat adult patients who have T315I-positive Philadelphia chromosome positive (Ph+) ALL or Ph+ ALL for whom no other tyrosine-kinase inhibitor therapy is indicated. TKIs specifically block the leukemia-causing effects of the *BCR-ABL* gene mutation in many patients. TKIs given alone would not result in cures for Ph-positive ALL patients, so these drugs are combined with chemotherapy. Studies are ongoing to learn the usefulness of this approach for Ph-positive ALL, and many results have been promising. New combinations of drugs are being studied in clinical trials for the treatment of Ph-positive ALL. For more information about clinical trials, see page 29.

Young Adults. Older adolescents and adults younger than 40 years are often called "young adults." Traditionally, treatment for this group has been similar to adult treatment protocols. However, clinical trials are looking into using a variety of pediatric protocol options. Some of these treatment options include combination chemotherapy using different dosing amounts; combination chemotherapy including rituximab (Rituxan®) and intensified doses of nonmyelotoxic drugs, such as prednisone, vincristine (Oncovin®) or PEG-asparaginase. Asparaginase *Erwinia chrysanthemi* (Erwinaze®) is offered as an alternative when the patient is allergic to PEG-asparaginase. Speak to your doctor or call an Information Specialist to learn about the different clinical trials that may be available to you.

Childhood Versus Adult Forms of ALL. ALL has an unusual pattern of age distribution (see Figure 1, page 7). The risk of developing ALL peaks between ages 1 to 4 years and then decreases until about age 50. At age 50, the incidence increases again, especially among men. As with other types of leukemia, incidence increases again as a person gets older.

The adult form of ALL is more resistant to treatment than the childhood form; however over the last few years several factors have contributed to longer remissions and prolonged survival for adult patients with ALL. These include

- Improved outcomes with allogeneic stem cell transplantation
- Use of tyrosine kinase inhibitors for Philadelphia chromosome (Ph+) ALL
- Use of intensified pediatric-like therapy for adolescents and young adults.

For patients with ALL that is resistant to treatment or who have relapsed, allogeneic stem cell transplantation may be the best option, if they are able to achieve complete remission before transplantation. Likewise, patients with high-risk disease are recommended for transplantation if it is unlikely that they will achieve remission with chemotherapy alone.

For ALL patients older than 60 years, patient performance status, other health issues and ALL risk features are all considered in developing a treatment plan. Age alone is not a reason to withhold treatment. 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 ALL 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 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 ALL cells. Occasionally, very elderly patients refuse treatment or are so ill from unrelated illnesses that treatment may be unreasonable.

There are new treatments under study for all ages and stages of disease.

Talk to your doctor about

- Whether treatment in a clinical trial is right for you.

Minimal Residual Disease (MRD). Sensitive molecular testing techniques permit the identification of small amounts of residual leukemia cells, known as minimal residual disease (MRD), at times when blood and marrow appear normal. This approach can be used if the leukemia cells have a detectable molecular abnormality or immunophenotype. It can also permit more sensitive follow-up of patients in remission and can help determine whether additional treatment is necessary. Studies in both children and adults with ALL have shown that there is a strong correlation between MRD and the risk or relapse. There is also a prognostic value to measuring MRD during and immediately after the initial induction therapy. The detection of MRD on day 29 of treatment (end of induction) may be useful in determining the need for additional induction therapy. In some pediatric institutions, doctors are checking for MRD on day eight as an indicator of slow early-responders.

Stem Cell Transplantation. Some patients may benefit from intensive chemotherapy alone followed by standard or reduced-intensity stem cell transplantation.

The decision to undergo a transplant should be discussed with your doctor. About 75 to 80 percent of children treated for ALL will not need a transplant. For an adult, the decision depends on the features of the leukemia and the patient's general health and age.

Which patients are likely to benefit from transplantation after their first complete remission is a question under study in clinical trials. Some of the main factors that influence the approach used are

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

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

Allogeneic Stem Cell Transplantation. This treatment uses donor stem cells to restore a patient's marrow and blood cells. For standard-risk patients in first remission, the choice between a transplant (standard or reduced-intensity) and continued chemotherapy is not clear.

For high-risk patients, an allogeneic transplant is an option for those patients in first remission who have a matched related or matched unrelated donor. Cord blood stem cells may be an alternative source for donor stem cells if an appropriate sibling or unrelated donor is not available. Allogeneic stem cell transplantation is a curative treatment option for some high-risk ALL patients in first remission.

Children who relapse less than six months following initial treatment or while in chemotherapy have a lower chance of a second remission. For these children and for children with refractory disease, transplantation with a matched related or matched unrelated donor may be considered. Cord blood stem cells may also be a source for the transplant. For children who do undergo transplantation, the use of unrelated human leukocyte antigen (HLA)-matched donors appears to be just as successful as it is for related HLA-matched donors (for example, siblings), making more donors available through stem cell transplantation registries.

Reduced-Intensity Allogeneic Stem Cell Transplantation. The benefits and risks of reduced-intensity allogeneic stem cell transplantation have not yet been clearly established for ALL patients. Patients who are too old or too ill to have a standard allogeneic stem cell transplant may be candidates for a reduced-intensity transplant if a suitable donor is available. The conditioning therapy used for a reduced-intensity transplant is of lower intensity than that for a standard allogeneic stem cell transplant; it does not completely inactivate the patient's immune system or treat the ALL as aggressively.

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 a "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 risk of graft-versus-host disease (GVHD) is an important consideration and a potentially disabling side effect.

Talk to your doctor about

- Whether a stem cell transplant is an option for you.

Autologous Stem Cell Transplantation. This procedure uses the patient's own stem cells to restore blood cell production. This type of transplant is not commonly used to treat ALL.

Refractory Leukemia or 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." Other patients achieve remission but then have a decrease in normal blood cells and a return of leukemia cells in the marrow. This situation is referred to as a "relapse."

With refractory leukemia, different drugs from those used in the first course of treatment may be administered in an effort to induce remission. Stem cell transplantation may be an option following remission that 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.

There are several drugs approved by the Food and Drug Administration (FDA) to treat relapsed or refractory ALL patients.

Nelarabine (Arranon®) is approved for patients with relapsed T-cell ALL. Clofarabine (Clolar®) is approved for patients who are between 1 and 21 years with relapsed or refractory ALL after they have received at least two prior chemotherapy regimens. Although treatment with clofarabine alone is not curative, it may lead to a temporary remission for the patient that is then followed by allogeneic stem cell transplantation, which may result in a cure. Clofarabine is also being studied in combination with other drugs in clinical trials for the treatment of children, adolescents and adults with relapsed or refractory ALL.

Liposomal vincristine (Marqibo®) is approved for adult patients with Ph chromosome-negative ALL who have relapsed two or more times, or whose leukemia has progressed following two or more regimens of therapy.

The following factors may increase the risk for relapse after initial treatments:

- Microscopic evidence of leukemia (minimal residual disease) after 20 weeks of therapy
- Age 30 years and older
- A high white blood cell count at the time of diagnosis
- Disease that has spread beyond the bone marrow to other parts of the lymphatic system, such as the spleen

- Certain genetic abnormalities, such as the presence of the Philadelphia chromosome or MLL (mixed-lineage leukemia) gene translocations
- The need for four or more weeks of induction chemotherapy in order to achieve a first complete remission.

Patients with one or more of these risk factors may be candidates for stem cell transplantation once they are in first remission. Talk to your doctor for more information.

Several drugs and drug combinations that can be used to treat ALL are being studied in clinical trials. LLS Information Specialists 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 an LLS-supported online clinical trial search service that offers patients and caregivers immediate access to listings of blood cancer clinical trials, by visiting www.LLS.org/clinicaltrials.

Talk to your doctor about

- Therapies under study in clinical trials for refractory or relapsed ALL.

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

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

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

Transfusion of red blood 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 ALL, the deficiency of neutrophils and monocytes (types of white blood cells) can lead to infection from bacteria and fungi normally present in the environment, on the skin, in the nose and mouth, on the gums, or in the 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 blood 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 it 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 blood 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, 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 blood 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 during urination; or frequent loose stools.

ALL patients are advised to receive certain vaccinations. It is recommended that children receive an annual influenza vaccine. Adult patients are advised to receive vaccinations for pneumococcal pneumonia and influenza. There are two types of pneumococcal vaccines available for adults: a pneumococcal polysaccharide vaccine (PPSV23) and a pneumococcal conjugate vaccine (PCV13). Immunizations using live organisms or with high viral loads, such as the herpes zoster or shingles vaccine, should not be administered. Your doctor can give you more information.

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
- Loss of appetite
- Fatigue.

Fortunately, drugs that counteract nausea and vomiting can be given to prevent or relieve these distressing side effects. Some ALL patients find that acupuncture treatments relieve chemotherapy-associated nausea and vomiting.

Some ALL patients may build up the concentration of uric acid in their blood as a result of a very high white blood cell count. The use of chemotherapy may also increase uric acid levels. Uric acid is a chemical in the cell. It 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 Side Effects of Drug Therapy*.

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 and Late Effects of Treatment* on page 27).

Talk to your doctor about

- Possible side effects and follow-up care.

Follow-up Care

Some of the tests that were done to diagnose ALL may be repeated to

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

After treatment, a patient who is in remission and has completed therapy continues to be examined regularly by his or her doctors. Careful periodic assessment of the patient's health, blood cell counts and, if indicated, marrow is required. As time progresses, assessments may be less frequent, but should continue indefinitely.

It is important to keep a record of your cancer treatment so that your doctor can follow up on specific late effects that may be associated with those treatments. This information would include your diagnosis, the names of chemotherapy drugs taken, radiation treatment information, surgery information, transplantation information, information about any other treatments, and the names and dates of any significant complications and the treatment received for those complications. This can help your doctor develop a follow-up schedule for you.

To find a follow-up clinic and other resources for child and adult survivors, contact our Information Specialists.

Both adults and children may experience difficulties when they return to their daily routines after such a long period of treatment. Getting support throughout this time, and for as long as needed, is important and will be helpful as you return to your "normal" life.

Long-Term and Late Effects of Treatment. Children and young adults who have been treated for ALL may be at increased risk for heart damage, other cancers and neurologic or cognitive problems. Patients should be seen by a primary care doctor for a general health examination 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 ALL 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 ALL patients are treated with an anthracycline, such as daunorubicin (Cerubidine®). 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.

Current prevention strategies for reducing heart damage include: limiting the cumulative dose of the anthracycline, altering drug schedules, using anthracycline structural analogs (chemical structure of the analog drug is modified to be less toxic but equally effective as the original drug) and liposomal encapsulated anthracyclines (the therapeutic agent has a special coating to reduce side effects), offering cardioprotective drugs and nutritional supplements.

Avascular necrosis and pain in the hip bones or shoulders may occur in some young patients after chemotherapy. Patients with these conditions may eventually require joint replacement surgery.

Sometimes cranial irradiation is used for patients with T-cell ALL or those who experience a relapse. Doctors are limiting the use of this treatment to avoid the risk of long-term or late effects such as neurocognitive impairment and the development of second cancers.

Stem cell transplantation is used to treat some patients with ALL. This treatment 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 second cancers is small.

Children may experience side effects of treatment, both in the short- and long-term, that can affect learning, including effects on growth, cognitive development and psychosocial development. Going back to school also brings new challenges to families whose main focus has been getting through treatment. By being aware of possible effects, parents can work with the school to help their child. See the free LLS publications *Coping With Childhood Leukemia and Lymphoma* and *Learning & Living With Cancer: Advocating for your child's educational needs*, which provide information about the challenges children may face and what can be done, the laws that protect your child and ways that schools can help.

Fertility. Recent studies show that both males and females treated for ALL as children or adolescents were not generally at increased risk for major complications during pregnancy or for infant malformation or death. Certain childhood cancers and treatments can increase the risk for preterm birth and low birth weight. Talk to your doctor for additional information.

Long-term and late effects can be managed. For more information see the free LLS publications *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma, Long-Term and Late Effects of Treatment in Adults* and *Understanding Side Effects of Drug Therapy.*

Talk to your doctor about

- Possible long-term and late effects and follow-up care.

Treatment Outcomes. A few decades ago there were very low cure rates in both children and adults diagnosed with ALL. Today, nearly 90 percent of children and 40 percent of adults can expect long-term, leukemia-free survival—and probable cure—with contemporary treatment. Currently, emphasis is placed not only on improving the cure rate but also on improving quality of life by preventing acute and late treatment-related complications, such as second cancers, cardiotoxicity and endocrinopathy.

"Relative survival" compares the survival rate of a person diagnosed with a disease to that of a person without the disease. In children under 15 years of age, the five-year relative survival rate has increased from 3 percent in 1964 to 89.2 percent in 2006 as a result of successful treatments made possible by clinical trials.

In adults, the probability of remission has increased dramatically in the last 10 years, and extended remissions are also more frequent. Several areas of research are likely to lead to further progress.

Research and Clinical Trials

New approaches under study in clinical trials for ALL treatment, many of which are being supported by LLS research programs, hold the promise of increasing the rate of remission and finding a cure for ALL.

Clinical Trials. Every new drug or treatment regimen goes through a series of 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. Patient participation in past clinical trials has resulted in the therapies we have today.

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 for patients with relapsed or refractory disease. A number of approaches are under study in clinical trials for the treatment of patients with ALL. Some of the objectives are

- To achieve a greater understanding of ALL cytogenetic abnormalities and how they affect prognosis
- To refine techniques to assess the high risk of relapse in individual patients to ensure that intensive treatment is given primarily to high-risk cases
- To find most effective combinations of chemotherapy drugs while reducing undesired side effects
- To develop treatment strategies to prevent or reverse chemotherapy resistance
- To refine stem cell transplants to increase effectiveness, reduce complications and determine which patients are most likely to benefit by this treatment
- To develop new and/or refine existing immunotherapy agents so that they can be used in frontline treatment
- To refine techniques for faster detection of minimal residual disease after induction therapy so that the patient's treatment plan can be more individualized.

Agents Under Study. The following are examples of specific agents under study in clinical trials for ALL.

Proteasome Inhibitor

- Bortezomib (Velcade®)—This drug, approved to treat myeloma and some types of lymphoma, is now being studied for the treatment of relapsed pediatric-ALL patients and patients with T-cell ALL.

Antimetabolite

- Clofarabine (Clolar®)—Already approved to treat pediatric ALL, it is now showing promising results in studies of adults with ALL. It is also being studied in combination with other drugs in clinical trials for the treatment of children, adolescents and adults with relapsed or refractory ALL.

Janus kinase (JAK) Inhibitor

- Ruxolitinib (Jakafi®)—Already approved to treat myelofibrosis patients, it is being studied in clinical trials in the treatment of pediatric refractory and relapsed ALL.

Immunotherapies

- Monoclonal antibodies rituximab (Rituxan®) and alemtuzumab (Campath®)—These drugs are already approved in the treatment of other blood cancers. They are currently being studied in clinical trials for ALL.
- Monoclonal antibody blinatumomab (AMG 103)—This new drug has shown promising results in early studies for adult ALL patients who have already received chemotherapy.

- Combination chemotherapy with or without Rituxan—This is being studied for the treatment of younger patients with B-cell ALL.
- Chimeric antigen receptor (CAR) therapy—This is another type of immunotherapy. The patient cells are removed through apheresis and modified in a laboratory so they can be reprogrammed to target tumor cells through a gene modification technique. The cells are then returned to the patient following chemotherapy. This technique is being studied in trials for pediatric ALL.

To learn more about clinical trials, you can read the free LLS publication *Understanding Clinical Trials for Blood Cancers*. We also encourage you to contact an Information Specialist and visit www.LLS.org for more information about specific treatments for ALL under study in clinical trials.

Normal Blood and Marrow

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 discharged 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 known as "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 tissues, where they can attack invading organisms and help combat infection. Eosinophils and basophils are 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.

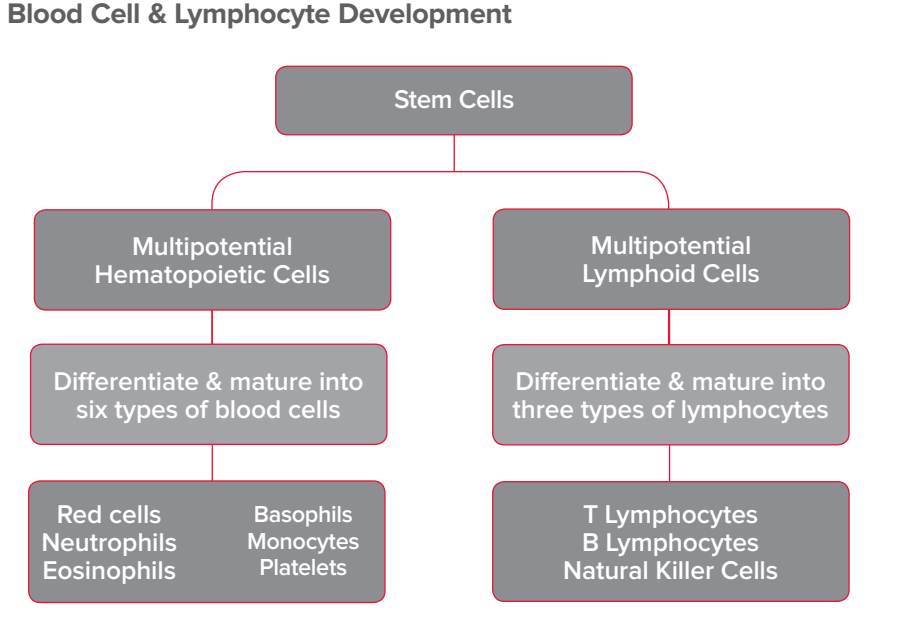

Figure 4. | **Stem cells** develop into blood cells (hematopoiesis) and lymphocytic cells.

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. The spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull contain the marrow that makes blood cells in adults. The process of blood cell formation is called "hematopoiesis." A small group of cells, the stem cells, develop into all the blood cells in the marrow by the process of differentiation (see Figure 4, on page 32).

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

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

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

The Lymphatic System

The Lymphatic System. The marrow is really two organs in one. The first is the blood cell-forming organ. The second is the lymphocyte-forming organ and is a part of the immune system.

The marrow produces three main types of lymphocytes:

- B lymphocytes (B cells), which make antibodies in response to foreign antigens, especially microbes
- T lymphocytes (T cells), which mature in the thymus. The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibody attaches to the microbe, making it possible for other white blood cells to recognize the antibody and pull it into the cell (ingest it) along with its attached microbe. The white blood cell then kills and digests the microbe
- Natural killer (NK) cells, which attack virus-infected cells without requiring antibody or other mediation. T cells and NK cells have other functions as well and are important elements in research efforts to design immunotherapies to treat lymphoma and other cancers.

The lymphocytes circulate through channels called "lymphatics," which connect the lymph nodes to each other throughout the body. The lymphatic channels collect into large ducts that empty into blood vessels. Lymphocytes enter the blood via these ducts. Most lymphocytes are found in the lymph nodes and other parts of the lymphatic system such as the skin; spleen; tonsils and adenoids (special lymph nodes); intestinal lining; and, in young people, the thymus.

Medical Terms

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

Allogeneic Stem Cell Transplantation. A treatment that uses donor stem cells to restore a patient's marrow and blood cells. The patient is given conditioning therapy (high-dose chemotherapy with or without total body radiation) to treat the blood cancer and "turn off" the immune system so that the donor cells are not rejected. For more information, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

Anemia. A decrease in the number of red blood cells and, therefore, in the hemoglobin concentration of the blood. 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 the specific foreign substances called "antigens." Antibodies coat, mark for destruction or inactivate foreign particles such as bacteria, viruses or harmful toxins. They can be used to identify and classify types of blood cancers or be altered to make them 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.

Autologous Stem Cell Transplantation. A treatment that uses a patient's own stem cells to delay the progression of certain blood cancers. The autologous transplantation process takes place after the patient achieves a complete response (remission), or a good partial response, to induction drug therapy. The stem cells are collected, then frozen for later use. After the patient receives conditioning therapy (intensive chemotherapy and/or radiation), the cells are thawed and infused back into the patient. For more information, see the free LLS publication *Blood and Marrow Stem Cell Transplantation*.

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

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.

Blast Cells. The earliest marrow cells identified by the light microscope. Blasts represent about one percent of normally developing marrow cells. In acute leukemias, abnormal blast cells (similar in appearance to normal blast cells) accumulate in large numbers, constituting up to 80 percent of all marrow cells. Abnormal blast cells interfere with the production of normal red blood cells, white blood cells and blood cells in the marrow.

Blood Cell Count. A laboratory test that requires a small blood sample to provide information about the types and numbers 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 blood cells, which carry oxygen; white blood cells, which principally prevent or combat infections; and platelets, which help prevent bleeding.

Bone Marrow. A spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation. See *Normal Blood and Marrow* on pages 31 through 33.

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 skin, the liquid sample is removed using a special needle inserted through the bone and into the bone marrow.

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

CBC. See Blood Cell Count.

Central Line (Indwelling Catheter). 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. See Port.

Central Nervous System (CNS) Prophylaxis. In certain types of leukemia, particularly acute lymphoblastic leukemia and acute monocytic leukemia with high blood cell counts, leukemic cells have a propensity for entering 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 lymphoblastic leukemia who enter remission are treated by placing appropriate chemotherapy in the fluid that bathes the spinal cord and brain to prevent the leukemia from returning in these sites. In some cases, x-ray therapy is administered to the head as well. These approaches are very effective in eliminating leukemia cells in the coverings of the brain and spinal cord.

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.

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. 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 due to chromosome breakage and rearrangement. See 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.

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.

Colony-Stimulating Factor. See Growth Factor.

Complete Blood Count (CBC). See Blood Cell Count.

Computed Tomography (CT) Scan. A technique for imaging body tissues and organs. X-ray transmissions are converted to detailed images using a computer to synthesize x-ray data. The images are displayed as a cross-section of the body at any level from the head to the feet.

Conditioning Treatment. Intensive therapy given to a patient in preparation for stem cell transplant. It typically includes cytotoxic drugs with or without total body radiation.

Cord Blood Stem Cells. Stem cells that are present in the blood drained from the placenta and umbilical cord after a baby is born. 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.

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.

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.

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

DNA. The genetic material in the cell.

DNA Repair Enzyme Inhibitors. Chemotherapy drugs that prevent certain cell proteins from working and make the DNA more susceptible to injury.

DNA Synthesis Inhibitors. Chemotherapy drugs that react with DNA to alter it chemically and keep it from permitting cell growth.

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

Erythrocytes. See Red Blood Cells.

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.

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 Fluorescence In Situ Hybridization (FISH).

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. One use of flow cytometry is to determine whether a sample of cells is composed of T cells or B cells. This permits the doctor 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.

Fluorescence In Situ Hybridization (FISH). A technique for studying chromosomes in tissue using DNA probes tagged with fluorescent molecules that emit light of different wavelengths (and different colors). The probes match to the chromosomes within the cells, and the chromosomes fluoresce in color.

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 the donor's marrow or blood cell suspension (the graft) against the tissues of the recipient (the host).The principal sites affected by GVHD are the skin, the liver and the gastrointestinal tract.

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

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 blood 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 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.

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 blood cells or white blood cells of various types. This is called "differentiation." The young or immature blood cells then further develop into fully functional blood cells. This is called "maturation." The mature cells leave the marrow, enter the blood and circulate throughout the body. Hematopoiesis is a process that is active normally throughout life since most blood cells live for short periods and must be replaced continuously.

Hemoglobin. The iron-containing pigment in red blood cells that carries oxygen to the tissue cells. A reduction in the number of red blood cells decreases the amount of hemoglobin in the blood. A decreased blood hemoglobin concentration is called "anemia."

HLA. The abbreviation for human leukocyte antigen(s). These antigens 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." Before transplantation takes place, tissue typing is performed in order to determine if the donor and recipient are compatible.

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.

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 lymphoblastic leukemic cells.

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. See Graft-Versus-Host Disease (GVHD).

Indwelling Catheter. See Central Line (Indwelling Catheter).

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 cancer cells are present in the meninges. This procedure is called "intrathecal therapy."

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 Blood Cells.

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

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

Lumbar Puncture. A procedure to remove spinal fluid from the space surrounding the spinal cord or to administer anticancer drugs to either prevent or treat leukemia or lymphoma of the coverings (meninges) of the central nervous system (CNS). Another term for lumbar puncture is "spinal tap."

Lymphatic System. The system comprising the lymph nodes, the thymus (in the first several decades of life), the lymphatic channels, the lymphatic tissue of the marrow, the gastrointestinal tract, the skin, the spleen, and the T, B and natural killer cells contained in those sites.

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.

Lymphoblast. The leukemic cell that replaces the normal marrow cell. Uncontrolled and exaggerated growth and accumulation of these leukemic cells means that they fail to function as normal blood cells.

Lymphocyte. A type of white blood 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/Macrophage.

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

Marrow. See Bone Marrow.

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 or flow cytometry-based 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. In cancer therapy, they can be used for the targeted delivery of drugs or radioactive substances to cancer cells.

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 blood 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 a monocyte leaves the blood and enters the tissue, it becomes a macrophage.

Multidrug Resistance (MDR). A characteristic of cells that makes them resistant to the effects of several different classes of drugs.

Mutation. An alteration in the structure of a gene that results from a change to the part of the DNA that represents the gene. See Oncogene.

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 blood cell.

Neutrophil. The principal phagocyte (microbe-eating cell) in the blood. This blood cell is the main cell that combats infections. A severe deficiency of neutrophils increases the patient's susceptibility to infection.

Oncogene. A mutated gene that is the cause of a cancer. Several subtypes of acute myeloid leukemia, acute lymphoblastic leukemia and lymphoma, and nearly all cases of chronic myeloid leukemia are associated with an oncogene.

Oncologist. A 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 blood cells, white blood cells and platelets.

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

Percutaneously Inserted Central Venous Catheter (PICC or PIC Line). A long, thin, flexible tube that is inserted into the body and can be left in place for weeks or even months for administration of medications, fluids and nutrition. It can also be used to obtain blood samples. The PICC eliminates the need for standard intravenous (IV) administration.

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

Petechiae. Pinhead-sized sites of bleeding in the skin. This type of bleeding results from a very low platelet count and is typically seen on the legs, feet, trunk and arms.

Phagocytes. Cells that readily eat (ingest) microorganisms such as bacteria or 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 the tissues in which an infection has developed.

Philadelphia Chromosome (Ph Chromosome). An abnormality of chromosome 22 found in the marrow and blood cells of patients with chronic myeloid leukemia and of some patients with acute lymphoblastic leukemia. The abnormality, a shortening of the long arm of this chromosome, was first observed and reported by doctors at the University of Pennsylvania; thus the name "Philadelphia chromosome." Since this discovery, the lost piece of chromosome 22 has been shown to stick (translocate) to chromosome 9 in most cases. Indeed, some of chromosome 9 also sticks (translocates) to chromosome 22. This is known as

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

PIC/PICC Line. See Percutaneously Inserted Central Venous Catheter (PIC/PICC Line).

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 blood cells) that stick to the site of blood vessel injury, aggregate and seal off the injured blood vessel to stop bleeding. "Thrombocyte" is a synonym for platelet and is often used as the prefix in terms describing platelet disorders, 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 collected from several unrelated donors and given as pooled, random-donor platelets. Sometimes the platelets are collected from a single donor using a special machine that separates the platelets from the blood.

Polymerase Chain Reaction (PCR). A technique to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be studied or determined. This technique has become useful in detecting a very low concentration of residual blood cancer cells, too few to be seen using a microscope. PCR can detect the presence of one blood cancer cell among 500,000 to 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 used with a central line (catheter) that allows access to a vein. The port is placed under the skin of the chest. To give medicines or nutrition or to take blood samples, 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.

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

Red Blood Cells. Blood cells that carry hemoglobin, which binds oxygen and carries it to the tissues of the body. Red blood cells are also called "erythrocytes."

Reduced-Intensity Stem Cell Transplantation. A form of allogeneic transplantation, now in clinical trials. In reduced-intensity transplantation (also called "nonmyeloblative stem cell transplantation") patients receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. For more information, 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 initial standard therapy for the disease. Newly diagnosed patients or relapsed patients may have refractory disease. In refractory leukemia, a proportion of malignant cells resist the damaging effects of one or several drugs. 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 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 cancer cells to grow despite exposure to a drug that ordinarily kills cells or inhibits their growth. Cells develop drug resistance in several different ways. See Multidrug Resistance (MDR).

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.

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

Sanctuary Sites. Areas in which it is difficult to get a sufficient concentration of chemotherapy to destroy leukemia cells. For example, in acute lymphoblastic leukemia, the coverings (meninges) of the brain and spinal cord and the testes are notable sanctuary sites.

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. Enlargement of the spleen is called "splenomegaly." Surgical removal of the spleen is known as "splenectomy."

Stem Cells. Primitive cells in marrow that are essential to the formation of red blood cells, white blood 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 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 decrease below normal in the 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. See Mutation.

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

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

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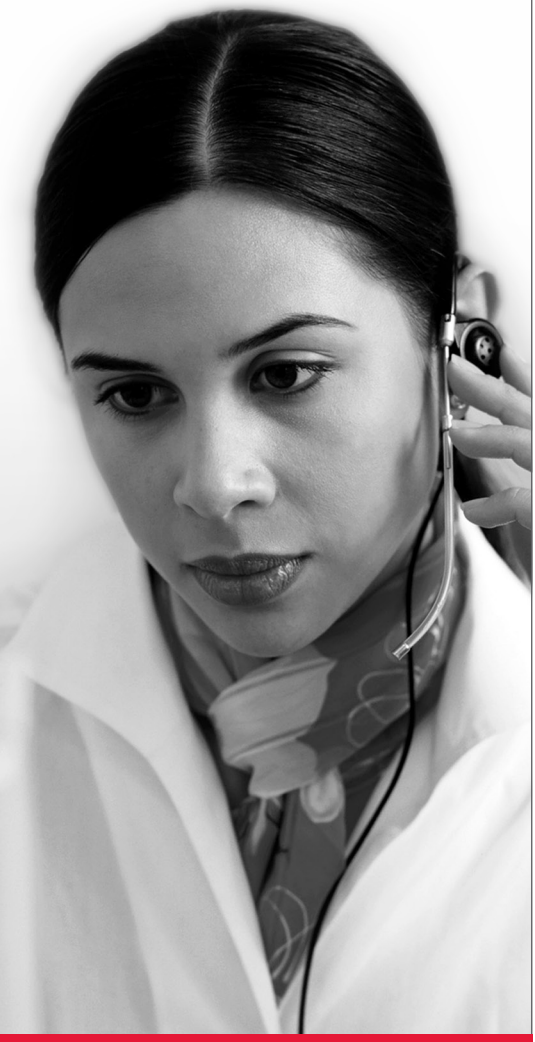

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