LEUKEMIA & LYMPHOMA SOCIETY®

PROVIDING THE LATEST INFORMATION FOR PATIENTS & CAREGIVERS

Acute Lymphoblastic Leukemia

Revised **2018**

Support for this publication provided by AMGEN SERVIER

A six-word narrative about living with blood cancer from patients in our LLS Community

Stay strong and keep moving forward. Find the positive in every day. Be your own best patient advocate. Changed my life for the better. Accept, learn and focus on present. Learning to live a different life. Sudden and life changing—be positive. Waiting, worrying, anxiousness/ happy I'm alive! Embrace a new normal each day. 5 years, 41 infusions, constant fatigue. Patience, positive attitude, hope and faith. Test to test, I will survive! Treatment, fatigue, treatment, fatigue and survival. Love life, live better every day. I don't look back only forward. So far, so good, live life. Meditation, mindfulness, wellness, faith, nutrition and optimism. Finding the joy while living with uncertainty. Watch, wait, treat, regroup, rest, re-energize. Blessed to be doing so well! Eye opening needed learning and healing. Feel great: uncertain travel plans annoying. Renewed faith, meditation, diet, mindfulness, gratitude. Watchful waiting can be watchful worrying. Scary, expensive, grateful, blessings, hope, faith. Thank god for stem cell transplants! Do not know what to expect. Extraordinarily grateful, I love my life. Diagnosed; frightened; tested; treating; waiting; hoping. I'm more generous, impatient less often. Embrace your treatment day after day. Live today, accept tomorrow, forget yesterday. Strength you never realized you had. Challenging to our hearts and minds. Life is what we make it. Live life in a beautiful way.

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- **Thousands of patients and caregivers sharing experiences and information, with support from knowledgeable staff**
- **Accurate and cutting-edge disease updates**
- **The opportunity to participate in surveys that will help improve care.**

Inside This Booklet

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Introduction

This booklet provides information about acute lymphoblastic leukemia (ALL) for patients and their families. Acute lymphoblastic leukemia is also known as “acute lymphocytic leukemia” and “acute lymphoid leukemia.”

People of any age can develop ALL, but most cases are diagnosed in patients younger than 20 years. It is the most common cancer found in children in the United States. Most cases of ALL are seen in children, but most deaths from ALL occur in adults.

Over the past several decades, advances in ALL testing and treatment have resulted in improved remission and cure rates, primarily among children. More work, however, remains to be done, and researchers are studying new therapies in clinical trials for patients of all ages.

At LLS, we know that the more you know about your disease, the better you can take care of yourself, your mind, your body and your health. This booklet provides information about ALL, explains tests and treatments that you may encounter, lists new research options and clinical trials, provides information about normal blood and bone marrow, and defines hard-to-understand terms.

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

We are here to help.

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Leukemia

Leukemia is a cancer of the blood and bone marrow. Most blood cells form in the bone marrow, the spongelike tissue in the center of most bones. Leukemia begins in a hematopoietic stem cell (an immature blood cell) in the bone marrow. The cell undergoes one or more malignant changes (mutations) and becomes a type of leukemia cell.

Leukemia cells differ from normal stem cells. They do not mature into healthy, functioning blood cells. They grow quickly and live longer than normal blood cells. They divide and copy themselves to make more and more leukemia cells. Over time, the leukemia cells either crowd out or suppress the development of normal healthy blood cells in the bone marrow, and they can spill out of the bone marrow into the bloodstream.

The four major types of leukemia are

- Acute lymphoblastic leukemia (ALL)
- Chronic lymphocytic leukemia (CLL)
- Acute myeloid leukemia (AML)
- Chronic myeloid leukemia (CML).

Disease progression (how quickly the disease gets worse) is one of the factors doctors consider when classifying leukemia. Leukemia can be either acute or chronic. Acute leukemia develops and progresses rapidly and typically gets worse quickly if not treated. Chronic leukemia usually progresses more slowly.

Leukemia is also classified by the type of blood cell that becomes cancerous. Leukemia is called "lymphoblastic" (or "lymphocytic") if the cancerous change begins in a young white blood cell called a "lymphoblast," a bone marrow cell that would normally develop into a lymphocyte. Leukemia is called "myeloid" or "myelogenous" if the cancerous cell change starts in early forms of myeloid cells—cells that develop into red blood cells, platelets and white blood cells (other than lymphocytes).

This booklet focuses on ALL, but there are other cancers that also start in lymphocytes that are called "lymphomas." The main difference between lymphoblastic leukemias and lymphoblastic lymphomas is the location of the cancer cells. Leukemias, such as ALL and CLL, generally affect the bone marrow and blood. In contrast, lymphomas are mostly located in lymph nodes or other lymphatic tissues or organs.

For more information on lymphoblastic lymphoma, see the free LLS booklet *Non-Hodgkin Lymphoma*. More general information about ALL is provided in the free LLS booklets, *Understanding Leukemia* and *The ALL Guide—Information for Patients and Caregivers*.

Acute Lymphoblastic Leukemia

How Acute Lymphoblastic Leukemia (ALL) Develops. In healthy bone marrow, stem cells become mature, adult blood cells through the process called "differentiation." When an immature lymphoid blood cell in the bone marrow becomes damaged and develops errors in its genetic material (DNA [deoxyribonucleic acid]), ALL develops. These genetic errors can give rise to a leukemic blast cell (lymphoblast) that is stuck in the earliest stages of cell development. This immature blast cell cannot mature into a functioning blood cell.

Genetic errors in the mutated cell tell the cell to keep growing and dividing when a healthy cell would typically stop dividing and eventually die. Every cell that arises from the initial leukemia blast also has the mutated DNA. As a result, the leukemia cells multiply uncontrollably. The leukemic blasts quickly accumulate in the bone marrow, suppressing the development of normal, healthy blood cells. As a result, there are too many leukemic blast cells that cannot function and too few mature, functioning blood cells.

By the time that ALL is diagnosed, the number of healthy blood cells (red blood cells, white blood cells and platelets) is usually lower than normal. This may result in infections, anemia and excessive bleeding.

The medical term for a	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)

Signs and Symptoms

Signs and symptoms are changes in the body that may indicate disease. A sign is a change that the doctor sees during an examination or on a laboratory test result. A symptom is a change that a patient can see and/or feel. A person who has signs or symptoms that suggest the possibility of leukemia is usually referred to a specialist. This is a hematologist-oncologist. A hematologist-oncologist is a doctor who has special training in diagnosing and treating blood cancers such as leukemia, lymphoma and myeloma.

The doctor will order tests to make a diagnosis (see *Diagnostic Testing* on *page 6*). The signs and symptoms of acute lymphoblastic leukemia (ALL) are also associated with a number of other, less serious diseases.

It is common for someone with ALL to feel a loss of well-being because of the underproduction of normal blood cells. This happens when the leukemia cells in the bone marrow crowd out the normal blood-making cells. Consequently, patients with ALL do not have sufficient numbers of mature red blood cells, white blood cells and platelets.

Symptoms of a low red blood cell count (anemia) include

- Fatigue
- Shortness of breath during normal physical activities
- Dizziness
- Pale complexion.

Symptoms of a low white blood count (leukopenia) include

- Frequent infections
- Fever.

Symptoms of a low platelet count (thrombocytopenia) include

- Bruising easily
- Prolonged bleeding from minor cuts
- The appearance of pinhead-sized red spots on the skin, called “petechiae”
- Frequent or severe nosebleeds
- Bleeding gums
- Blood in the urine.

Other general symptoms of ALL include

- Night sweats
- Discomfort in bones or joints
- Enlarged spleen, liver or lymph nodes
- Pain or feeling of fullness below the ribs
- Unexplained weight loss or loss of appetite.

Diagnostic Testing

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.

Medical History and Physical Examination. If a person has signs or symptoms of leukemia, the doctor will take a thorough medical history. The history may include information about past illnesses, injuries, treatments and medications. Some illnesses run in families, so the doctor may also ask about the health of the patient's blood relatives. The doctor will want to know about the patient's current symptoms and conduct a physical examination. During the examination, the doctor may listen to the patient's lungs and heart and carefully examine the body for signs of infection and disease. To check the internal organs, the doctor may also feel (palpate) different parts of the patient's body. For example, the doctor may feel the abdomen to see if the patient has an enlarged liver or spleen. In men, the doctor may also examine the patient's testicles to see if there are any masses. The doctor may also check for signs of infection, for example, enlarged lymph nodes. The doctor will likely palpate areas such as the armpits and the neck to check for enlarged lymph nodes.

Blood and Bone Marrow Tests. If the signs and symptoms suggest that the person may have leukemia, the doctor will test the blood and bone marrow. The findings from blood and bone marrow tests are used for making diagnosis and treatment decisions. The doctor may also refer the patient to a hematologist-oncologist, a doctor who has special training in diagnosing and treating blood cancers.

Blood samples are generally taken from a vein in the patient's arm. Bone marrow aspiration and biopsy are two procedures used to examine bone marrow cells for abnormalities and these tests are generally done at the same time. The samples are usually taken from the patient's hip bone (after medicine has been given to numb the skin). Bone marrow has both a solid and a liquid component. For a bone marrow aspiration, a special hollow biopsy needle is inserted through the hip bone and into the marrow to remove (aspirate) a liquid sample of cells. For a bone

marrow biopsy, a specialized wider needle is used to remove a core sample of solid bone that contains marrow.

At the laboratory, a hematopathologist will examine the blood and bone marrow samples. A hematopathologist is a doctor who has special training in identifying diseases by studying cells under a microscope.

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

People with acute lymphoblastic leukemia (ALL) may have a high number of white blood cells and a low number of red blood cells and platelets. This is because too many lymphoblasts are being made in the bone marrow. These lymphoblasts crowd the bone marrow so that too few normal, healthy blood cells are made.

Even if CBC findings suggest leukemia, an ALL diagnosis is usually made only after a hematopathologist has examined a sample of bone marrow cells.

Blood Chemistry Profile. This is a blood test that measures the levels of certain substances released into the blood by organs and tissues in the body. These substances include electrolytes (such as sodium, potassium and chloride), fats, proteins, glucose (sugar), uric acid and enzymes. Blood chemistry test findings indicate how well a person's kidneys, liver and other organs are working. These test results, although not used to diagnose leukemia, may show an abnormal amount of a particular substance in the blood that may be a sign of disease or some other health problem. A blood chemistry profile also provides helpful information about any potential organ damage caused by leukemia cells or ALL treatments.

Coagulation Test. This is a blood test that measures how well the blood is able to clot and determines whether there are deficiencies in some proteins, such as fibrinogen.

Cell Assessment. A hematopathologist will examine a sample of blood cells or bone marrow cells under the microscope to determine the size, shape, and type of cells as well as to identify other features of the cells. A significant finding is the appearance of the cells—whether the cells look more like normal, mature blood cells or more like abnormal, immature blood cells (blast cells). See **Figure 1** on *page 8*.

The percentage of blast cells identified in the blood sample is very important. Typically, there are no blast cells in the blood and no more than 5 percent of the cells in the bone marrow are blast cells. Generally, a diagnosis of ALL requires a finding that shows that 20 percent or more of the cells in the bone marrow are lymphoblasts.

Acute Lymphoblastic Leukemia (ALL) Cells

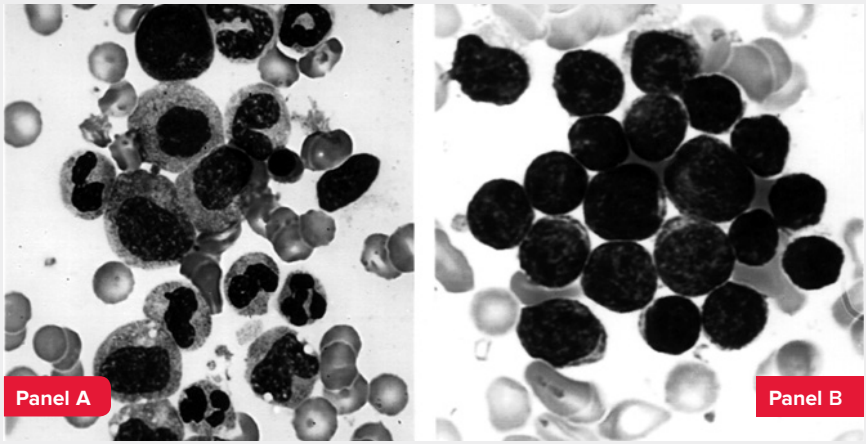

Figure 1. **Panel A** shows a photograph of developing cells in healthy marrow. The variation in the appearance of the cells is characteristic of normal marrow. **Panel B** shows a photograph of marrow cells from a patient with acute lymphoblastic leukemia. An unvaried appearance characterizes the leukemic blast cells.

Flow Cytometry. This test is used to classify cells in a blood sample. The classification is based on the types of antigens, or markers/proteins, on the surface of the cells. The pattern of the surface proteins is called the "immunophenotype." A sample of bone marrow is often used for this test, but a blood sample may also be used. The sample of cells is treated with special man-made antibodies that only stick to the cells if the cells have a specific antigen on them. The cells are then passed through a laser beam. The cells with antibodies attached to them will give off light. Leukemia cells are different from healthy cells; they can have different antigens on their surface depending on whether the cells are myeloid or lymphoid and their stage of development.

Flow cytometry helps to confirm an ALL diagnosis. It is also used to determine the type of lymphocytes in which ALL originated and to assess the maturity of the cells. Flow cytometry is also used to check treatment results.

Genetic Tests. The following tests are used to identify, examine and measure chromosomes and genes.

Cytogenetic Analysis (Karyotyping). In this test a hematopathologist uses a microscope to examine the chromosomes inside of cells. Karyotyping is used to look for abnormal changes in the chromosomes of the leukemia cells of patients with ALL.

Normal human cells contain 23 pairs of chromosomes for a total of 46 chromosomes. Each pair of chromosomes is a certain size, shape and structure. In many cases of ALL, the chromosomes of leukemia cells have abnormal changes that can be seen under a microscope such as translocations and extra chromosomes. A translocation occurs when a piece of one chromosome breaks off and attaches to another chromosome. Sometimes pieces from two different chromosomes will trade places. This results in a "fusion gene," an abnormal gene that is formed when two different genes are fused together.

Cytogenetic testing is done using either a bone marrow or a blood sample. The leukemia cells in the sample are allowed to grow in the laboratory and then they are stained prior to examination. The stained sample is examined under a microscope and then photographed to show the arrangement of the chromosomes (the karyotype). The karyotype will show if there are any abnormal changes in the size, shape, structure or number of chromosomes in the leukemia cells. See **Figure 2**, *below*.

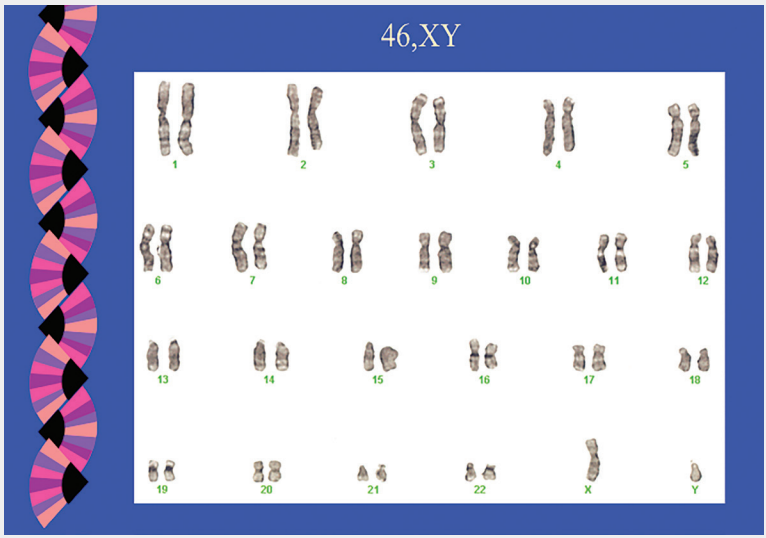

Figure 2. This figure shows a normal male karyotype. (Courtesy of Dr. Dong Chen, hematopathologist, Mayo Clinic, Rochester, MN)

Cytogenetic analysis provides information that is important when determining a patient's treatment options and prognosis. This information can predict how the disease will respond to therapy. For example, a translocation between chromosomes 9 and 22 is associated with a diagnosis of Philadelphia chromosome-positive (Ph+) ALL, a subtype of ALL that is treated differently than other subtypes.

Fluorescence in situ Hybridization (FISH). This is a cytogenetic laboratory technique that is used to identify and examine genes or chromosomes in cells and tissues. In cases of ALL, doctors use FISH to detect certain abnormal changes in the chromosomes and genes of leukemia cells. Pieces of DNA (deoxyribonucleic acid) that contain special fluorescent dyes are made in the laboratory and added to the leukemia cells on a glass slide. When the pieces of DNA bind to specific genes or areas of chromosomes on the slide, they light up when viewed under a fluorescent microscope. Many abnormal changes can be seen with a microscope, but FISH testing can also detect changes that are too small to be seen on basic cytogenetic tests. A FISH test is not, however, a general screening tool. It has one disadvantage—the doctor must select specific chromosomes or genes to examine before running the test.

Polymerase Chain Reaction (PCR). A PCR is a very sensitive laboratory technique that is used to detect and measure some genetic mutations and chromosomal changes that are too small to be seen with a microscope. Polymerase chain reaction testing essentially increases or "amplifies" small amounts of specific pieces of either RNA (ribonucleic acid) or DNA to make them easier to detect and measure. This test can find a single leukemia cell among more than 500,000 to one million normal cells. Polymerase chain reaction testing is one method used to determine the amount of minimal residual disease (MRD), the small amount of cancer cells left in the body after treatment. This testing can be done on a bone marrow or a blood sample.

Spinal Fluid Test. The following test examines the fluid in the spinal column for ALL cells.

Lumbar Puncture. Acute lymphoblastic leukemia can spread to the cerebrospinal fluid (CSF), the fluid that flows around the brain and spinal cord. In order to determine whether or not leukemia cells have spread to this area, a sample of the CSF is tested.

A lumbar puncture (also called a "spinal tap") is a procedure that is used to collect the CSF from the spinal column. After the area over the spine in the lower part of the back has been numbed with a local anesthetic, a thin needle is inserted between two bones (vertebrae) and into the CSF. A sample of the fluid is withdrawn and examined under a microscope to look for leukemia cells that may have spread to the brain and spinal cord.

Imaging Tests. These tests create images of the inside of the body.

Computed Tomography (CT) Scan. A CT scan uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the body. At times, leukemia may grow outside the bone marrow—most commonly in lymph nodes. A CT scan may be used to look for enlarged lymph nodes, liver or spleen caused by an accumulation of leukemia cells in the chest, abdomen and pelvis.

Magnetic Resonance Imaging (MRI) Scan. This scan uses magnetic fields and radio waves to create images of the body's organs and tissue. Magnetic resonance imaging scans are also used to visualize the brain and spinal cord. An MRI scan of the head and/or spinal cord should be done if a patient has symptoms (such as headache or seizures) that suggest that ALL cells may have spread to the brain and spinal cord.

Ultrasonography. This procedure uses high-energy sound waves to examine tissues and organs inside the body. Testicular involvement can occur so an ultrasound examination of the scrotum (the external sac that contains the testicles) may be needed to see if a mass is present.

Echocardiogram. A computerized image of the heart is created by bouncing sound waves (ultrasound) off internal tissues or organs of the chest. An echocardiogram shows the heart's size, shape and position as well as its internal structures. It also shows how the heart is beating and how it is pumping blood. Some treatments for ALL can damage the heart so the doctor may want to evaluate a patient's heart and cardiac function in order to plan the best treatment.

See the free LLS booklet *Understanding Lab and Imaging Tests* for more information about these tests.

Diagnosis and Cell Classification

The diagnosis of acute lymphoblastic leukemia (ALL) generally requires the identification of 20 percent or more leukemic blasts of lymphoid origin (lymphoblasts) in the bone marrow. The ALL subtype is determined based upon a patient's laboratory results.

Subtypes of ALL. The subtypes of ALL are based on certain features of the leukemia cells. The ALL subtype is an important factor in treatment planning. Depending on the ALL subtype, the doctor will decide which drugs, drug combinations and drug dosages are indicated and determine the duration of treatment that is most appropriate for the patient. The treatment plan may also include other types of treatment (such as a stem cell transplant) that may be needed to achieve the best outcomes.

Immunophenotyping. Leukemia cells can be classified by the unique set of proteins found on their surface. These unique sets of proteins are known as "immunophenotypes."

Based on the immunophenotype of the leukemia cell, the World Health Organization (WHO) classifies ALL in the following ways (see **Table 1** on *page 13*):

- B-cell lymphoblastic leukemia/lymphoma. This subtype of ALL begins in immature cells that would normally develop into B-cell lymphocytes. This is the

most common ALL subtype. Among children, B-cell lineage ALL constitutes approximately 88 percent of cases. Among adults, B-cell lineage represents 75 percent of cases. Within the B-cell lineage, the cell surface markers differ according to the stage of cell maturation.

- Before 2008, the WHO classified B-cell lymphoblastic leukemia as "precursor B-lymphoblastic leukemia," and this term is still often used to distinguish it from mature B-cell ALL. Mature B-cell ALL is now referred to as "Burkitt leukemia." The treatment for Burkitt leukemia is based on therapy for non-Hodgkin lymphoma and is different than the treatment used for ALL. **For more information on Burkitt leukemia, see the free LLS booklet *Non-Hodgkin Lymphoma*.**

- T-cell lymphoblastic leukemia. This subtype of ALL originates in immature cells that would normally develop into T-cell lymphocytes. This subtype is less common, and it occurs more often in adults than in children. Among adults, T-cell lineage represents about 25 percent of cases. Among children T-cell lineage represents approximately 12 percent of cases.

Cytogenetic Changes. In addition to classifying ALL as either B-cell or T-cell lymphoblastic leukemia, the WHO further classifies ALL based on changes to certain chromosomes and genes (see **Table 2** on *page 14*). This identification of specific cytogenetic abnormalities is critical for disease evaluation, risk stratification and treatment planning.

Translocations are the most common type of genetic change associated with ALL. In a translocation, the DNA (deoxyribonucleic acid) from one chromosome breaks off and becomes attached to a different chromosome. This results in a "fusion gene," an abnormal gene that is formed when two different genes are fused together.

Another type of genetic change in ALL is the result of numerical abnormalities. A numerical abnormality is either the gain or loss in the number of chromosomes from the normal 46. A change in the number of chromosomes can affect growth, development and the functioning of body systems. Approximately 25 percent of children with ALL have hyperdiploidy.

About 75 percent of adult and childhood cases of ALL can be classified into subgroups based on the chromosome number or DNA analysis, specific chromosomal rearrangements and molecular genetic changes. Not all patients who have ALL exhibit the same chromosome changes. Some changes are more common than others and some have a greater effect on the patient's prognosis.

World Health Organization Classification of Acute Lymphoblastic Leukemia (ALL)

B cell lymphoblastic leukemia/lymphoma

- B-cell lymphoblastic leukemia/lymphoma, not otherwise specified (NOS)
- B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
  - B-cell lymphoblastic leukemia/lymphoma with translocation (t)(9;22)(q34.1;q11.2); *BCR-ABL1*
  - B-cell lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
  - B-cell lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
  - B-cell lymphoblastic leukemia/lymphoma with hyperdiploidy
  - B-cell lymphoblastic leukemia/lymphoma with hypodiploidy
  - B-cell lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH*
  - B-cell lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
  - *Provisional entity: B-cell lymphoblastic leukemia/lymphoma, BCR-ABL1–like*
  - *Provisional entity: B-cell lymphoblastic leukemia/lymphoma with iAMP21*

T-cell lymphoblastic leukemia/lymphoma

- *Provisional entity: early T-cell precursor lymphoblastic leukemia*

Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma

Table 1. The classification of acute lymphoblastic leukemia types created by the World Health Organization (WHO).

Common Chromosomal and Molecular Abnormalities in Acute Lymphoblastic Leukemia (ALL)

Abnormality	Gene(s) Associated	Frequency in Adults (%)	Frequency in Children (%)	Associated Prognosis
Hyperdiploidy (more than 46 chromosomes)	—	7	25	Favorable prognosis
Hypodiploidy (fewer than 46 chromosomes	—	2	1	Poor prognosis
Translocation (t)(9;22) (q34;q11) "Philadelphia" or "Ph" chromosome Translocation (t) between chromosomes 22 and 9	*BCR-ABL1*	25	2-4	Favorable prognosis with contemporary therapy
Translocation (t) between chromosomes 12 and 21: t(12;21) (p13;q22)	*ETV6-RUNX1 (TEL-AML1)*	2	22	Favorable prognosis
t(v;11q23) [eg, t(4;11), t(9;11)], t(11;19)	*KMT2A(MLL)*	10	8	Poor risk
Translocation (t) between chromosomes 1 and 19 t(1;19)(q23;p13)	*TCF3-PBX1 (E2A-PBX1)*	3	6	
t(5;14)(q31;q32)	*IL3-IGH*	< 1	< 1	
t(8;14), t(2;8), t(8;22)	*c-MYC*	4	2	Favorable prognosis with short-term intensive therapy
t(1;14)(p32;q11)	*TAL-1* Abnormalities observed exclusively in T-cell lineage	12	7	
t(10;14)(q24;q11)	*HOX11 (TLX1)*[a]	8	1	
t(5;14)(q35;q32)	*HOX11L2*[a]	1	3	
t(11;14)(q11)[eg, (p13;q11), (p15;q11)]	*TCRα* and *TCRσ*	20-25	10-20	
BCR-ABL1-like	various	10-30	15	Poor prognosis

Abnormality	Gene(s) Associated	Frequency in Adults (%)	Frequency in Children (%)	Associated Prognosis
iAMP21 (intrachromosomal amplification of chromosome 21)	Three or more extra copies of *RUNX1* on an abnormal chromosome 21	2% in pediatric B-ALL, mostly in older children and adolescents (median age 9 years)	Uncommon	Poor prognosis
ETP (early T-cell precursor)	Various[a]	2	10%-15% of T-cell ALL in children	No significant difference from non-ETP T-ALL
Ikaros	*IKZF1*	25-35	12-17	Poor prognosis
[a]Abnormalities observed exclusively in T-cell lineage.				

Table 2. Adapted from NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia, 2018.
Cytogenetic changes are sometimes abbreviated. For example,
- t– a translocation between chromosomes.
- inv– an inversion in a chromosome.
- q– the long arm of a chromosome (the lower half)
- p– the short arm of a chromosome (the upper half)

Prognostic Factors/Treatment Planning

Certain factors can affect a patient's outlook or prognosis. These are called "prognostic factors." Doctors use certain prognostic factors to help predict how a patient's acute lymphoblastic leukemia (ALL) is likely to respond to treatment. These factors help doctors to plan the most appropriate initial treatment regimen as well as help them determine either when or whether to consider stem cell transplantation as a treatment option.

Prognostic factors for children with ALL include

- Age: The leukemia cells in infants who are less than 1 year and children older than 10 years tend to be more resistant to treatment, so stronger treatments may be needed to kill the leukemia cells.
- White blood cell count: Children with white blood cell counts of $50x10^9$L or greater for B-cell lineage at the time of diagnosis also need stronger treatment.
- Certain changes in the chromosomes or genes that can make the leukemia cells either easier or harder to treat. See **Table 2** on *page 14* and **Table 3** on *page 16*.
- The presence of leukemia cells in the cerebrospinal fluid and/or the testicles at the time of diagnosis.

- How the patient responds to initial induction therapy. Patients who have a better response to induction therapy typically have a lower risk of disease relapse.

Children with high-risk ALL or very high-risk ALL usually receive more intense treatment than children with standard-risk ALL.

Prognostic factors for adults with ALL include

- Age: The leukemia cells in older patients tend to be more resistant to treatment. Patients older than 35 years have decreased remission duration and a harder time tolerating chemotherapy.
- White blood cell count: Patients with white blood cell counts greater than $30x10^9$/L for B-cell lineage and greater than $100x10^9$/L for T-cell lineage at the time of diagnosis generally have decreased remission duration.
- Certain changes in the chromosomes or genes can make the leukemia cells easier or harder to treat. See **Table 2** on *page 14* or **Table 3** *below*.
- Whether the leukemia cells are found in the cerebrospinal fluid at the time of diagnosis.
- How the patient responds to initial induction therapy. Patients who have a better response to induction therapy typically have a lower risk of relapse.

Cytogentic Risk Groups

Risk Groups	Cytogenetics
Good risk	Hyperdiploidy (51-65 chromosomes); cases with trisomy of chromosomes 4 and 10, appear to have the most favorable outcome); t(12;21)(p13;q22): *ETV6-RUNX1*
Poor risk	Hypodiploidy (<46 chromosomes); t(v;11q23): t(4;11) and other *KMT2A* rearranged t(11q23);t(9;22)(q34;q11.2): *BCR-ABL1* (defined as “high risk” in the pre-TKI era); complex karyotype (5 or more chromosomal abnormalities); Ph-like ALL; amplification occurring within (intrachromosomal) chromosome 21 (iAMP21)

KEY: ALL, acute lymphoblastic leukemia; Ph-like, Philadelphia-like; TKI, tyrosine kinase inhibitor.

Table 3. The National Comprehensive Cancer Network (NCCN) Acute Lymphoblastic Leukemia Guidelines; 2018.

Treatment

Drugs may have been approved since this book was printed.
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A patient has two options for treatment: standard care or a clinical trial. It is important to talk to the healthcare team about the best treatment option.

A diagnosis of acute lymphoblastic leukemia (ALL) is associated with a wide range of outcomes. Therefore, it is essential to seek treatment in a center where doctors are experienced in the care of patients who have ALL. Patients who have ALL need treatment as soon as possible after diagnosis. If time allows, however, a patient may want to seek a second opinion. A second opinion may help a patient to feel more confident about the chosen treatment plan.

Talk to your doctor about

- Your treatment options and the results you can expect from treatment
- The results you might expect with standard therapy
- 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 of infertility.

See the free LLS booklet *Fertility* Facts for more details.

Chemotherapy. The current "standard" treatment for ALL is long-term chemotherapy. It typically lasts for about 2 to 3 years and it is often intense, especially in the first few months of treatment. The most common treatment regimens use a combination of more than one anticancer drug.

Chemotherapy drugs kill fast-growing cells throughout the body including cancer cells and normal, healthy cells. Different types of chemotherapy drugs work in different ways to eradicate leukemia cells or stop new leukemia cells from forming. Therefore, more than one chemotherapy drug is frequently used.

Chemotherapy is often given in treatment cycles. Each cycle is made up of a number of days of treatment followed by a number of days of rest. The rest days allow the body time to recover before the next treatment cycle begins. Cycles vary in length depending on which drugs are used.

Some chemotherapy drugs may be injected into a vein. An intravenous (IV) infusion is a slow injection into a vein that may take a few hours or it may take several days (a continuous infusion). Often, doctors give IV chemotherapy through a thin soft tube called a "central venous line," "catheter," or "central line." The

central line is often attached to a "port" that is placed surgically under the skin in the patient's upper chest and permits access to the central line.

In general, there are three phases of treatment. These are the induction, consolidation (also called "intensification") and maintenance therapies. Consolidation and maintenance are therapies given after remission (also called "postremission" therapies).

Induction Therapy. The initial phase of chemotherapy is called "induction." The specific drugs, the dosages used and timing of administration depend on several factors, including the patient's age, the specific features of the leukemia and the overall health of the patient.

The goal of induction therapy is to destroy as many cancer cells as possible in order to achieve (induce) a remission.

Induction regimens for ALL generally use a combination of drugs that include **vincristine**; anthracyclines (**daunorubicin, doxorubicin**); and corticosteroids (**prednisone, dexamethasone**) administered either with or without **asparaginase** and/or **cyclophosphamide**. See **Table 4** on *page 20*.

Typically, the severity of the disease and the side effects of this initial therapy result in a hospital stay of 4 to 6 weeks. Children and 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.

For some children, the hospital stay is the first time they have been away from home for an extended period of time. Providing age-appropriate information to your child about the illness and its treatment will help him or her build trust in you and the members of the treatment team. Talking about his or her fears and concerns will also help your child to feel more comfortable.

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, see the free LLS booklet *Coping With Childhood Leukemia and Lymphoma*.

At the end of induction therapy, doctors will check to see whether the patient has achieved a complete remission. A complete remission is achieved when

- No leukemia cells are detected in the bone marrow (with a microscope)
- No more than 5 percent of cells in the bone marrow are blast cells
- No blast cells are in the bloodstream
- Blood cell counts are back to normal
- All signs and symptoms of ALL are gone.

Even when a complete remission is achieved, some leukemia cells that cannot be seen with a microscope may still remain in the body. The presence of these cells is referred to as "minimal residual disease (MRD)." Patients who have achieved remission after initial treatment for this type of ALL, but have MRD, are at increased risk of disease relapse.

After a patient achieves a complete remission, postremission therapy is given to kill every remaining leukemia cell in the body. **Blinatumomab (Blincyto®)** is approved by the US Food and Drug Administration (FDA) to treat adults and children who have B-cell precursor ALL, are in remission, but still have MRD. 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.

Central Nervous System (CNS) Prophylaxis and Treatment. Although the presence of leukemia cells in the cerebrospinal fluid at diagnosis is not common (found in only 3 to 7 percent of cases), a large percentage of patients (50 percent or more) eventually develop CNS leukemia without the routine administration of CNS-targeted therapy, also called "central nervous system prophylaxis." CNS prophylaxis is administered to prevent leukemia cells from spreading to the area around the brain and the spinal cord and is typically given to all patients throughout the entire course of ALL treatment—during the induction phase, the consolidation phase and the maintenance phase.

Central nervous system-directed therapy may include

- Intrathecal chemotherapy. In this treatment, anticancer drugs are injected into the fluid-filled space between the thin layers of tissue that cover the brain and spinal cord. These drugs may include **methotrexate, cytarabine** and corticosteroids **(prednisone, dexamethasone).**
- High-dose systemic chemotherapy. In this treatment, anticancer drugs travel through the blood to cells all over the body. These drugs may include **methotrexate, cytarabine, 6-mercaptopurine** and **asparaginase.**
- Cranial irradiation. Radiation therapy to the brain.

In most doctors' practices, cranial irradiation for pediatric patients (except in patients who have CNS leukemia or a CNS relapse) is not used. Treatment without radiation decreases the patient's chances of experiencing long-term and late effects, such as organ damage, the development of second cancers and neurocognitive impairment.

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

Antitumor Antibiotics

- Daunorubicin (Cerubidine®)
- Doxorubicin (Adriamycin®)
- Mitoxantrone (Novantrone®)
- Idarubicin (Idamycin®)

DNA-Repair Enzyme Inhibitor

- Etoposide (VP-16; VePesid®, Etopophos®)

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

Antimetabolites

- Clofarabine (Clolar®)
- Cytarabine (cytosine arabinoside, ara-C; Cytosar-U;® DepoCyt®)
- Fludarabine (Fludara®)
- Hydroxyurea (Hydrea®)
- 6-mercaptopurine (Purinethol,® Purixan®)
- Methotrexate (Xatmep®; Abitrexate®; Trexall®)
- Nelarabine (Arranon®)
- 6-thioguanine (thioguanine; Tabloid®)

Drugs That Prevent Cells From Dividing

- Vincristine (Oncovin®)
- Vincristine sulfate liposome (Marqibo®)

Synthetic Hormones (Corticosteroids)

- Prednisone
- Methylprednisolone
- Dexamethasone

Immunotherapies

- Alemtuzumab (Campath®)
- Rituximab (Rituxan®)
- Ofatumumab (Arzerra®)
- Blinatumomab (Blincyto®)
- Inotuzumab ozogamicin (Besponsa®)
- Tisagenlecleucel (Kymriah®)

Table 4. This table includes drugs used for treatment and drugs being studied in clinical trials for the treatment of ALL.

Drugs may have been approved since this book was printed.
Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Postremission Therapy (Consolidation and Maintenance Therapy). "Post-remission therapy" refers to ALL treatments given to patients after their disease is in a complete remission. Residual leukemia cells remain after remission, so the optimal treatment for ALL patients 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. The second phase of chemotherapy is called "consolidation" therapy. This phase is also known as "intensification," therapy. Consolidation therapy is given once ALL is in remission. The goal of consolidation is to kill any remaining leukemia cells in the body. During this phase, the chemotherapy drugs are given in higher doses than those given during the induction phase. Consolidation therapy is usually given in cycles over 4 to 6 months. The goal of this phase of treatment is to reduce the number of leukemic cells still remaining after induction therapy.

The combination of drugs and the duration of therapy for consolidation regimens vary but can consist of combinations of drugs similar to those drugs used during the induction phase.

Treatment protocols may include one or two intensified treatments that are similar to the ones used during induction. These intensified treatments are also known as "delayed intensification" treatments.

Generally, several chemotherapy drugs are combined to help prevent the leukemia cells from developing drug resistance.

Some of the drugs used in the consolidation treatment phase include

- High-dose **methotrexate**
- **Cytarabine**
- **Vincristine**
- **6-mercaptopurine**
- **Blinatumomab (Blincyto®)**, given IV, is FDA approved for the treatment of adults and children with B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. It is also approved for the treatment of relapsed or refractory B-cell precursor ALL.
- **Inotuzumab ozogamicin (Besponsa®)**, given IV, is FDA approved for the treatment of adults with relapsed or refractory B-cell precursor ALL.
- **Cyclophosphamide**
- **Asparaginase**
- Corticosteroids **(prednisone, dexamethasone).**

Maintenance. The third phase of ALL treatment is called "maintenance." The goal of maintenance therapy is to prevent disease relapse after induction and consolidation therapy. Most maintenance drugs are given orally and, typically, patients are treated in an outpatient setting. They receive lower doses of chemotherapy drugs and, as a result, tend to have less severe side effects. Maintenance therapy usually lasts for about 2 years for adults and 2 to 3 years for children. In some cases, postremission chemotherapy also includes drugs that were not used during induction treatment. Most maintenance regimens include

- **6-mercaptopurine** (administered daily)
- **Methotrexate** (administered weekly)
- **Vincristine**
- Corticosteroids **(prednisone, dexamethasone)**
- Intrathecal chemotherapy.

Side Effects of Chemotherapy. Most ALL treatment side effects are temporary and subside once the body adjusts to therapy or when therapy is completed. If side effects become severe, patients may be treated on an inpatient basis.

Low Blood Cell Counts. Acute lymphoblastic leukemia decreases the production of normal blood cells. In addition, chemotherapy can be toxic to both normal blood cells and ALL cells. This results in a severe deficiency in the patient's number of red blood cells, white blood cells and platelets.

Transfusions of red blood cells and platelets are almost always needed for several weeks during treatment. After that, the blood cell counts usually return to normal levels.

Many side effects of chemotherapy are caused by low white blood cell counts. Drugs known as "growth factors" may be given to stimulate the bone marrow to make new white blood cells to reduce the chance for serious infections. The growth factors used most frequently are the granulocyte-colony stimulating factors (G-CSFs **filgrastim [Neupogen®]** and **pegfilgrastim [Neulasta®]**) and the granulocyte-macrophage colony-stimulating factor (GM-CSF) **sargramostim [Leukine®]**).

Infection. During treatment for ALL, the deficiency of white blood cells can lead to infections from bacteria and fungi that are 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 cells lining the mouth and intestines, making it easier for bacteria to enter the bloodstream. When the white blood cell count is low, antibiotics to prevent bacterial infection and drugs that prevent fungal and viral infections are given.

The patient is at increased risk for infection, so the medical staff, family and friends need to practice frequent and vigorous handwashing and take other precautions to avoid exposing these patients to bacteria, viruses and other infection-causing agents. Caregivers for patients who have central lines or ports need to be meticulous in the cleaning of insertion sites and catheters.

Patients at home should seek medical attention immediately if any signs of infection develop. A temperature of 101°F or higher, or the onset of chills, may be the only sign of infection in a patient who has a very low white blood cell count. Other signs of infection may include persistent coughing, sore throat, pain during urination, or diarrhea.

Patients who have ALL are advised to receive certain vaccinations. It is recommended that children receive an annual influenza (flu) vaccine. Adult patients are advised to receive vaccinations for influenza and pneumococcal pneumonia. Immunizations using either live organisms or those with high viral loads, such as the herpes zoster or shingles vaccine **Zoster Vaccine Live (Zostavax®),** should not be given to ALL patients. If a family member or a friend receives a live vaccine, the patient should not go near him or her for a period of time.

Tumor Lysis Syndrome. Patients with ALL may be at high risk for developing a condition called "tumor lysis syndrome (TLS)," especially those who had very high white blood cell counts before induction therapy. Tumor lysis syndrome can occur after treatment of a fast-growing cancer like leukemia. As the leukemia cells die, they break apart and release their contents into the bloodstream and change the normal balance of chemicals in the blood. This can overwhelm the kidneys because they cannot get rid of the substances all at once.

Uric acid is one of the chemicals released by the dying cancer cells. Very high levels of uric acid and other chemicals can cause severe damage to the kidneys and heart. If untreated, TLS can lead to heart arrhythmias, seizures, loss of muscle control, acute kidney failure and even death. Patients are constantly monitored for the development of this condition and are given drugs such as **allopurinol (Zyloprim®)** or **rasburicase (Elitek®)** to prevent or lessen the effects of TLS.

Other Side Effects. Chemotherapy drugs affect cells that divide quickly, which is why they work against cancer cells. They also affect other healthy cells in the body that divide quickly, such as the lining of the intestines, the skin and hair follicles. Common side effects may include

- Mouth sores
- Diarrhea
- Hair loss
- Rashes

- Itchy skin
- Nausea and vomiting
- Headaches
- Loss of appetite
- Fatigue
- Neuropathy-numbness, tingling or muscle weakness (usually in the hands or feet).

Generally, these short-term side effects go away once a patient has completed treatment. Fortunately, drugs that counteract nausea and vomiting can be given to either prevent or relieve this distressing side effect.

The use of corticosteroids, such as **prednisone** and **dexamethasone**, is a main component of virtually every ALL induction regimen. These drugs are also frequently incorporated into consolidation and maintenance regimens. Acute side effects of corticosteroids may include hyperglycemia and corticosteroid-induced diabetes. Patients should be monitored for glucose control. The development of gastric ulcers is another potential side effect of corticosteroid therapy. Proton-pump inhibitor drugs that reduce stomach acid are recommended during corticosteroid therapy to reduce risk of gastric ulceration.

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

Sometimes, a drug or a drug combination causes side effects that continue after treatment ends. Some effects may be long-lasting (see *Long-Term and Late Effects of Treatment* on *page 38*).

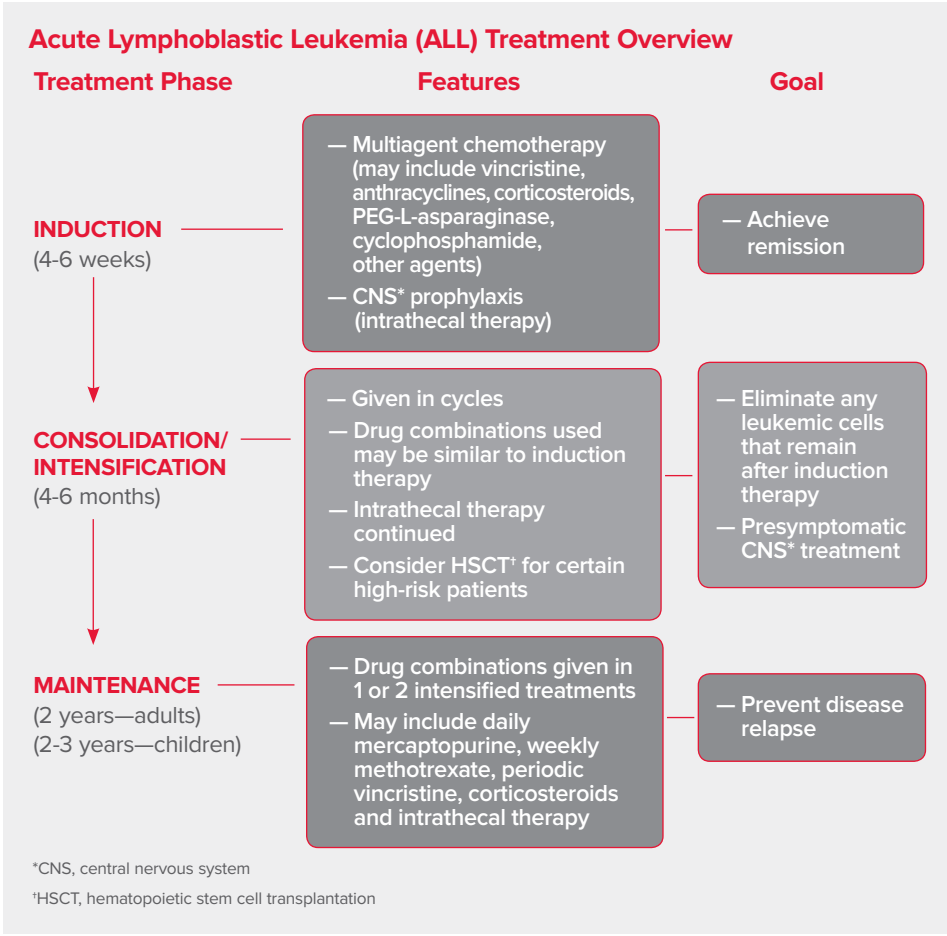

Figure 3. This figure provides general information. There are many different ALL treatment approaches. Speak to your doctor to develop a specific treatment plan for either you or your child. Adapted from NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia, 2018.

Targeted Therapy. Targeted therapy uses drugs or other substances that target and attack specific cancer cells but are less likely to harm normal cells. Some targeted therapies block the action of certain enzymes, proteins or other molecules that are involved in the growth and division of cancer cells. Other types of targeted therapies help the immune system destroy cancer cells or deliver toxic substances directly to cancer cells and kill them. Targeted therapies may have fewer side effects than other types of cancer treatments.

Tyrosine Kinase Inhibitors (TKIs). About 25 percent of adults and about 3 percent of children have an ALL subtype called "Ph-positive ALL" (also known as either "Ph+" or "Philadelphia chromosome-positive ALL"). In Ph+ ALL the Philadelphia chromosome contains the abnormal *BCR-ABL* fusion gene that makes an abnormal protein that helps leukemia cells to grow. Tyrosine kinase

inhibitors are used to treat Ph+ ALL by blocking (inhibiting) the BCR-ABL protein from sending signals that cause leukemia cells to form.

Tyrosine kinase inhibitors alone are generally not used to treat ALL. Instead, they are added to a combination chemotherapy regimen. These drugs are taken daily as pills. The following TKIs are available to treat Ph+ ALL:

- **Imatinib (Gleevec®),** taken by mouth, is approved for adult patients with relapsed or refractory Ph+ ALL and pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy
- **Dasatinib (Sprycel®),** taken by mouth, is approved for adults with Ph+ ALL with resistance or intolerance to prior therapy.
- **Ponatinib (Iclusig®),** taken by mouth, is approved for the treatment of adult patients with T315I-positive Ph+ ALL.

Common side effects of TKIs include low blood counts, abnormal bleeding and pain, nausea and vomiting, diarrhea, fatigue, rashes, headaches and muscle, bone and joint pain. They may also cause fluid to collect under the eyes, and in the hands, feet or lungs. Uncommon, but serious, side effects include a change in the rhythm of the heart, blood vessel narrowing or blood clot formation.

Dasatinib may cause fluid to collect around the lungs. Ponatinib side effects may include blood clots, narrowing of blood vessels, heart attack, stroke, liver problems, or inflammation of the pancreas.

Immunotherapy. Immunotherapy is a treatment that uses substances that can stimulate and/or suppress the immune system to help the body fight cancer. There are immunotherapy treatments that target cluster of differentiation (CD) surface antigens expressed by ALL blast cells. **Table 5**, *below*, provides the frequency of ALL subtypes by CD designation in children.

Relative frequency of acute lymphoblastic leukemia (ALL) subtypes in children

ALL Type	Frequency	CD Designation
B-precursor ALL	70%	10, 19, 20, 22, 24
B-precursor with myeloid features	10%	Also express: 11, 13, 14, 15, 33, 34, 41, 42
Mature B cell	2% to 5%	10±, 19, 20, 22, 25, slg
T cell	16%	2, 3, 4, 5, 7, 8

KEY: ALL: acute lymphoblastic leukemia; CD: cluster designation; slg: surface immunoglobulin.

Table 5. Source: Overview of the presentation and diagnosis of acute lymphoblastic leukemia in children and adolescents. *UpTo Date*. Last updated June 2018, Accessed July 2018.

Monoclonal Antibodies. Monoclonal antibodies are proteins that are made in the laboratory. They can bind to substances in the body, including cancer cells. Most attach to one specific substance. These drugs can be used alone to destroy cancer cells or to carry drugs, toxins or radioactive substances directly to the cancer cells. They are also used to target clusters of differentiation (CD) surface antigens expressed by ALL blast cells. One of the most promising new approaches for treating ALL relies on monoclonal antibodies to target CD19, CD20, CD22, CD33 and CD52 on ALL cells.

- **Blinatumomab (Blincyto®).** Blinatumomab is a bispecific antibody used to treat either relapsed or refractory B-cell ALL in adults and children in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. It is also approved for relapsed or refractory B-cell precursor ALL. Blinatumomab binds to a protein, CD19, which is found on the surface of most healthy B cells and most lymphoblastic leukemia B cells.

  Blinatumomab is a liquid that is administered slowly through a vein (IV) as a continuous infusion over 28 days. Hospitalization is typically recommended for the first few days of treatment. Side effects of blinatumomab include

  - Fever
  - Headache
  - Infection
  - Nausea
  - Diarrhea
  - Swelling
  - Neurological complications such as seizures, confusion, disorientation, slurred speech, and loss of balance.

- **Rituximab (Rituxan®).** Rituximab is a monoclonal antibody that is being studied to treat certain patients with B-cell ALL. It binds to CD20, a protein that is found on the surface of healthy B cells and on the lymphoblastic B cells of approximately one half of adults with B-cell ALL. When rituximab binds to CD20, it signals the cell to die. Rituximab is not used alone to treat ALL, but it is added to a chemotherapy regimen. Some studies have shown that the addition of rituximab to standard chemotherapy improved survival among adults with CD20-postive ALL. Side effects may include infections, chills, fatigue, body aches and low blood cell counts.
- **Inotuzumab ozogamicin (Besponsa®).** Inotuzumab ozogamicin is a monoclonal antibody linked to a chemotherapy drug used to treat relapsed or refractory B-cell ALL. Inotuzumab ozogamicin targets CD22, a cell surface antigen expressed on the cancer cells of most B cell ALL patients. When inotuzumab ozogamicin binds to the CD22 antigen on B cells, it enters the cell where the chemotherapy drug **calicheamicin** is released causing the cell to die.

Inotuzumab ozogamicin, administered as an IV infusion, can be given in an outpatient setting for appropriate patients. Common side effects include increased risk of infections, bleeding, fatigue, fever, nausea, headache, and abdominal pain.

Chimeric Antigen Receptor (CAR) T-Cell Therapy. **Tisagenlecleucel (Kymriah®)** is FDA approved for the treatment of patients up to age 25 years who experience a second or later relapse or refractory B-cell ALL.

Tisagenlecleucel treatment is designed to help the body's own immune system fight cancer. Each dose is made specifically for an individual patient. It is made using the patient's own T cells (white blood cells that help the body to fight infections and cancer). The T cells are collected from the patient and then modified with a new gene containing a CAR protein so that the T cells can identify and kill leukemia cells with CD19 on their surface. These modified cells are infused back into the patient's bloodstream to kill the cancer cells.

For more comprehensive information on CAR T-Cell Therapy, see the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy* Facts.

Stem Cell Transplantation. Some patients may benefit from stem cell transplantation. The goal of stem cell transplantation is to cure the patient's cancer by destroying the cancer cells in the bone marrow with high doses of chemotherapy and then replacing them with new, healthy blood-forming stem cells. The healthy blood stem cells will grow and multiply forming new bone marrow and blood cells. There are two main types of stem cell transplantation. They are

- Allogeneic—patients receive stem cells from a matched or a partially mismatched related donor or an unrelated donor.
- Autologous—patients receive their own stem cells.

Stem cell transplantation is not used as the first or primary treatment for ALL. It may be used as a treatment for high-risk ALL patients or for patients who do not respond to treatment.

Stem cell transplantation is a complex treatment. It can cause serious side effects that can be life threatening so it may not be a treatment option for every ALL patient. The decision to undergo a transplant should be discussed with the doctor. The doctor will consider many factors, including the patient's age, general health, certain prognostic factors, previous treatments, and if the patient has a well-matched donor.

Allogeneic Stem Cell Transplantation. Allogeneic stem cell transplantation is the most common type of stem cell transplantation used to treat ALL. In preparation for the transplant, patients are given strong doses of chemotherapy, either with or without radiation, to kill the remaining leukemic cells in their bodies. This is called "conditioning therapy." Then, patients receive infusions of the donor stem cells. Allogeneic transplantation uses healthy blood-forming cells from an HLA-matched or partially mismatched family member, an unrelated donor, or an umbilical cord blood unit. The donated stem cells restore the bone marrow's ability to form new blood cells.

An allogeneic stem cell transplantation creates a new immune system for the patient. The immune system helps the body fight infections and other diseases. The new immune system has the potential to recognize and attack any remaining cancer cells. The transplanted immune cells (the graft) see the leukemia cells in the body as foreign and destroy them. This is called the "graft-versus-leukemia (GVL) effect."

Allogeneic stem cell transplantation, compared to other treatment approaches, is associated with a higher rate of side effects and mortality. It may, however, be considered for patients with higher-risk ALL, based on cytogenetic and molecular test results. The decision to perform an allogeneic transplantation also depends on the age of the patient and the patient's understanding of the potential benefits and risks. The upper age limit for transplantation varies by treatment center; many centers use age 60 or 65 years as the age limit for allogeneic transplantation and 70 years for reduced-intensity allogeneic transplantation.

Most children treated for ALL will not need a transplant, but allogeneic stem cell transplantation is an option for children who have very high-risk factors or persistent disease.

For adults, studies show that allogeneic stem cell transplantation may benefit high-risk and intermediate-risk patients who are younger than 60 years and have a human leukocyte antigen (HLA)-matched sibling donor. Timing of allogeneic stem cell transplantation is one of the most important factors influencing transplant outcomes, so it is very important to start a donor search as soon as possible after diagnosis in order to identify a suitably matched related or unrelated donor.

After the transplantation of the stem cells, one possible serious side effect is graft-versus-host disease (GVHD). Graft-versus-host disease occurs when the transplanted donor immune cells (the graft) identify the cells in the recipient's body (the host) as foreign and attack them. The parts of the body most commonly damaged by GVHD include the skin, liver, stomach, intestines and eyes. Graft-versus-host disease can develop either within weeks after transplantation or much later. A doctor can order medications that can help to prevent or minimize GVHD.

Reduced-Intensity Allogeneic Stem Cell Transplantation. A reduced-intensity stem cell transplantation is a type of allogeneic transplantation. It may be a treatment option for older patients who cannot tolerate the high doses of chemotherapy used in preparation for a standard allogeneic stem cell transplantation. The conditioning therapy in a reduced-intensity transplant uses lower doses of chemotherapy and/or radiation to prepare the patient for the donor cells. The therapy reduces the number of cancer cells, but it does not completely destroy the patient's bone marrow. As in a standard allogeneic transplantation, the white blood cells from the donor may also recognize any remaining leukemia cells as foreign and destroy them. Over time, if the transplant is successful, the donor's stem cells will 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.

As is the case with standard allogeneic stem cell transplantation, the risk of GVHD is an important consideration and a potentially disabling side effect.

Autologous Stem Cell Transplantation. A procedure in which stem cells are removed from a cancer patient, stored, and then given back to the patient after the patient undergoes intensive chemotherapy either with or without radiation therapy.

An autologous transplant is not commonly used to treat a patient who has ALL, but it may be a treatment option for an ALL patient participating in a clinical trial.

Talk to your doctor about

- A stem cell transplant. Ask whether it is a treatment option for either you or your child.

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

Special Treatment Considerations

Philadelphia Chromosome—Positive (Ph+) Acute Lymphoblastic Leukemia (ALL). About 25 percent of adults and only about 3 percent of children who have ALL have a subtype called "Ph-positive ALL" (also known as either "Ph+" or "Philadelphia chromosome-positive ALL"). Patients with this ALL subtype have a chromosome alteration that results in a specific mutation of the *BCR-ABL* gene. These patients are treated with the tyrosine kinase inhibitors (TKIs) combined with chemotherapy.

This combination has become the standard of care for Ph+ ALL patients. New combinations of drugs are being studied in clinical trials for the treatment of Ph-positive ALL. See *Tyrosine Kinase Inhibitors* on *page 25* for more information on TKIs.

Philadelphia Chromosome-like (Ph-like) ALL. Philadelphia chromosome-like ALL is a subgroup of B-cell ALL that has genetic features similar to Ph+ ALL but lacks the *BCR-ABL* fusion gene that defines Ph+ ALL. This subtype of ALL is more likely to be seen in males and patients with Down syndrome and occurs four to five times more frequently in children and young adults than Ph+ ALL. The prevalence of Ph-like ALL is 10 percent in children with standard-risk ALL is over 25 percent in young adults with standard risk ALL. It is associated with an unfavorable prognosis. Recent studies that analyzed the genetic profile of patients with Ph-like ALL have suggested that using TKIs and other targeted therapies may help these leukemias and this is an area of active clinical research.

Childhood Versus Adult Forms of ALL. The adult form of ALL is more resistant to treatment than the childhood form; however, over the past few years, several factors have contributed to longer remissions and prolonged survival for adult patients who have ALL. These include

- Improved outcomes with allogeneic stem cell transplantation
- Use of TKIs for the treatment of Ph+ ALL
- Use of intensified pediatric-like therapy for adolescents and young adults.

For ALL patients older than 60 years, patient performance status, other health issues and ALL risk features are taken into consideration when a treatment plan is being developed. Age alone is not a reason to withhold treatment. 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 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.

The main goal of therapies targeting patients older than 60 years is to maintain efficacy while minimizing toxic side effects. 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.

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

A new type of immunotherapy called "chimeric antigen receptor (CAR) T-cell therapy" uses the patient's own immune cells to target and eliminate cancerous cells. It is being studied in the treatment of refractory and relapsed ALL in both children and adults. For more information on this therapy, *see Immunotherapy on page 28* and **see the LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy* Facts.**

Talk to your doctor about

- Treatment in a clinical trial.

Older Adolescents and Young Adults (AYA). The AYA population is generally regarded as patients aged 15 to 39 years. Historically, the AYA population has been treated with either a pediatric ALL regimen or an adult ALL regimen depending on the treatment institution. Adult treatment regimens and pediatric treatment regimens are different in the following ways:

- Pediatric regimens are more intense and complex than those given to older adults.
- Pediatric regimens tend to use more **pegaspargase, vincristine** and corticosteroids. In contrast, adult regimens tend to use more **cyclophosphamide** and anthracyclines, such as **doxorubicin** and **daunorubicin**.
- Pediatric treatments are given for longer periods of time. Central nervous system treatment is started earlier and given longer. Some children receive maintenance therapy for up to 3 years while adults tend to receive 2 years of maintenance therapy.

Researchers in clinical trials have started looking into the use of a variety of pediatric protocol options for the AYA patients. They have found that AYA patients treated on pediatric protocols have improved rates of survival compared to the same-aged patients treated on adult ALL protocols.

Refractory Leukemia or Relapsed Leukemia. Some patients have residual leukemic cells in their marrow even after intensive treatment. The disease is then referred to as "refractory leukemia." Other patients achieve remission but they have decreased numbers of normal blood cells and a return of leukemia cells in the marrow. The disease is considered relapsed.

Ph+ ALL. For patients with relapsed or refractory Ph+ ALL, there are several treatment options.

A patient may receive a different TKI. Before a patient starts treatment, *BCR-ABL* gene mutation testing should be done. This test looks for mutations in the *BCR-ABL* fusion gene that affects how well certain TKIs work. Each TKI works in a slightly different way. One TKI may be able to counteract a mutation that another TKI cannot. Many Ph+ ALL patients receive **imatinib (Gleevec®)** during induction therapy. For those patients whose disease has relapsed **dasatinib (Sprycel®),** or **ponatinib (Iclusig®)** may be treatment options.

The TKI may be given alone, it may be part of a chemotherapy regimen or, in some cases, it may be combined with a corticosteroid. If the TKI is part of a chemotherapy regimen, typically the regimen will be different from the one used during initial therapy. For some older patients who cannot tolerate chemotherapy, a TKI and a corticosteroid may be an option. If ALL does not respond to treatment with TKIs, doctors may recommend regimens for relapsed or refractory Ph-negative ALL. These include

- **Blinatumomab (Blincyto®).** This may be an treatment option for patients whose ALL has not responded to two or more TKIs.
- **Inotuzumab ozogamicin (Besponsa®).** This is a treatment option for adults with either relapsed or refractory B-cell ALL.
- **Tisagenlecleucel (Kymriah®).** This treatment is for B-cell ALL patients who are younger than 26 years and have refractory disease or have had two relapses.

An allogeneic stem cell transplantation is also an option for healthy patients who have an available donor. Some older patients and those in poor health may not be able to tolerate such an intense treatment.

Ph-Negative ALL. For patients with relapsed or refractory Ph-negative ALL, there are also several treatment options.

One option is to use different drugs than those used during the patient's first induction regimen. These may include

- **Blinatumomab**
- **Inotuzumab ozogamicin**

- Combination regimens that include several chemotherapy drugs, some of which may have been given in the past. Examples of such include
  - **Augmented hyper-CVAD.** This regimen includes cyclophosphamide, vincristine, doxorubicin (Adriamycin®), dexamethasone, pegaspargase, methotrexate and cytarabine.
  - **MOpAD**-(methotrexate, vincristine [Oncovin®], pegylated L-asparaginase, and dexamethasone) with **rituximab** for CD20-positive disease.

However, there are different chemotherapy regimens that may use different drug combinations. The following drugs may be part of these regimens:

- **Nelarabine** for patients with T-cell ALL
- **Clofarabine**
- **Liposomal vincristine (Marqibo®)**, for the treatment of adult patients with Ph- ALL in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies
- **Tisagenlecleucel**.

With refractory leukemia, different drugs from those used in the first course of treatment may be administered in an effort to induce remission. Following remission, stem cell transplantation may be an option and it may result in a more durable remission. In patients whose disease has relapsed, the duration of the remission, the patient's age and the cytogenetic findings in the leukemia cells influence the approach to therapy.

Talk to your doctor about

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

Research and Clinical Trials

New approaches are under study in clinical trials for acute lymphoblastic leukemia (ALL) treatment. Many of the trials are being supported by LLS research programs and hold the promise of increasing the rate of remission and finding a cure for ALL.

Clinical Trials. ALL patients are encouraged to explore participating in a clinical trial. Clinical trials test new drugs and treatments before they are approved by the Food and Drug Administration (FDA) as standard treatments. Every new drug or treatment regimen goes through a series of phases of clinical trials before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by 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.

Clinical trials are designed to be accurate and very safe. There are clinical trials for newly diagnosed patients, for patients with advanced disease, and for patients who are either resistant to their medications or are unable to tolerate them.

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. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

Research Approaches. Scientific research is being done to learn more about ALL: how best to treat it and how to provide the best care to people diagnosed with ALL.

Agents Under Study. Here are examples (and some descriptions) of specific agents that are under study in clinical trials for ALL.

Proteasome Inhibitor

- **Bortezomib (Velcade®)**—This drug, approved to treat myeloma and mantle cell lymphoma, is now being studied in combination with other standard chemotherapy drugs for the treatment of relapsed or refractory ALL. It is also being studied for treating newly diagnosed pediatric patients with T-cell ALL.

Antimetabolite

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

Janus Kinase (JAK) 1 and 2 Inhibitor

- **Ruxolitinib (Jakafi®)**—Already approved to treat myelofibrosis and polycythemia vera patients, this drug is being studied in clinical trials in the treatment of pediatric refractory and relapsed ALL. It is also being studied in combination with several chemotherapy drugs in the treatment of children with Philadelphia-like (Ph-like) ALL and *CRLF2* and *JAK* alterations.

Special Chemotherapy Combination

- **Augmented Hyper-CVAD**—The hyper-CVAD (**cyclophosphamide**, **vincristine**, **doxorubicin (Adriamycin®)** and **dexamethasone**) combination is a well-established treatment regimen for adult ALL. The augmented hyper-CVAD formulation was designed in 2011 and it includes intensified doses of vincristine, and dexamethasone along with **asparaginase**. Researchers are studying the efficacy of this combination for ALL treatment with other drugs including **decitabine (Dacogen®)**.

Immunotherapy

- **Tisagenlecleucel (Kymriah®)**—Chimeric antigen receptor (CAR) T-cell therapy is a type of immunotherapy that consists of engineering patients' own immune cells to first recognize and then attack cancer cells. Tisagenlecleucel (Kymriah®) is FDA approved for patients up to age 25 with relapse or refractory B-cell ALL. It is the result of reprogramming the patient's own T cells to locate and destroy cells that have the CD19 protein on their surface. In some cases, the leukemia cells do not have CD19 on the surface. Such cells can evade tisagenlecleucel and multiply. A research goal is to find other markers on leukemia cells that can be targeted along with the CD19, such as CD22.

For more information on this type of therapy, see the LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy* Facts.

Patients and their families who want to learn more about clinical trials can contact an LLS Information Specialist at (800) 955-4572.

Related Disease

Mixed Phenotype Acute Leukemia (MPAL). Mixed phenotype acute leukemia, also known as "mixed lineage leukemia," is a subtype of acute leukemia of ambiguous lineage. It is two forms of leukemia combined: acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Mixed phenotype acute leukemia represents 2 to 5 percent of all acute leukemias affecting patients of all ages and comprises several different subtypes. The best approach to treatment has not been defined. There is no standard therapy for MPAL and, in general, the disease is associated with a poor prognosis. This is due to difficulty in correctly identifying this type of leukemia, its rare incidence, lack of experience in treating it and its resistance to both ALL and AML therapy. The reasons underlying this resistance are not yet clear but may be related to the high percentage of MPAL patients with cytogenetic abnormalities. Developing the best treatment approach involves considering a variety of factors including the patient's age, medical history, presence of other relevant medical conditions and the characteristics of the leukemic cells, as determined by immunophenotyping and cytogenetic and molecular studies. It is also important to determine whether a patient has a Philadelphia chromosome-positive (Ph+) subtype. This subtype accounts for about 25 percent of all cases of MPAL. Patients with Ph+ MPAL are treated with age-specific ALL chemotherapy in combination with a tyrosine kinase inhibitor (TKI), followed by allogeneic stem cell transplantation if needed. For patients with a non-Ph+ MPAL subtype, the treatment consists of either an ALL regimen or a combination of ALL and AML therapy, possibly followed by consolidation treatment with an allogeneic transplant, when a donor is available.

Follow-up Care

After a patient completes treatment for acute lymphoblastic leukemia (ALL) and is in remission, follow-up tests are given to check on how well the treatment worked and to look for signs of relapse. The tests also check on how well the patient's organs are working. This is important since ALL and its treatment can damage organs. During the first year, a patient will undergo frequent testing, but follow-up tests are given less often during the second and third years. As time goes on, less frequent testing and check-ups may be required, but scheduled assessments should be continued indefinitely.

The National Comprehensive Cancer Network (NCCN) recommends the following tests during the first 3 years after treatment ends:

- During the first year after the completion of therapy
  - A complete physical examination (including testicular examination) every 1 to 2 months
  - Blood tests (a complete blood count [CBC] with differential) every 1 to 2 months
  - Liver function tests until normal values are achieved
  - Bone marrow aspiration, lumbar puncture and an echocardiogram, as clinically indicated.
- During the second year after the completion of therapy
  - A complete physical examination (including testicular examination) every 3 to 6 months
  - Blood tests (a CBC with differential) every 3 to 6 months.
- During the third year after the completion of therapy
  - A complete physical examination (including testicular examination) every 6 to 12 months
  - Blood tests (a CBC with differential) every 6 to 12 months or as directed by a specialist.

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

Both adults and children may experience difficulties when they return to their daily routines after a long period of treatment. Getting support throughout this time, and for as long as needed, is important.

Long-Term 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 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

- The 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**. 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.

Osteonecrosis, also called “avascular necrosis” (reduced blood flow to the bones) and bone pain are potential long-term side effects associated with corticosteroid therapy. Osteonecrosis often affects weight-bearing joints, such as the hip bones and/or knees and seems to have a higher incidence among adolescents, (most likely due to skeletal growth) than in younger children or adults. To monitor patients who are at risk of developing this condition, routine measurements of calcium and vitamin D levels should be obtained and periodic imaging evaluation should be considered.

Sometimes, cranial radiation is used for patients with obvious central nervous system (CNS) disease involvement or those whose disease relapses. Doctors are limiting the use of this treatment (and using drug-therapy alternatives as much as possible) to avoid the risk of long-term or late effects such as neurocognitive impairment and the development of second cancers.

Children may experience side effects of treatment, both in the short and long term. These side effects can affect learning, growth, cognitive development and psychosocial development. When children return to school, there will be new challenges facing families whose main focus, up to that point, had been getting through treatment. By being aware of possible side effects, parents can work with school personnel to help their children cope and manage schoolwork.

These and other possible long-term and late effects can be managed. For more information, see the following free LLS booklets *Long-Term and Late Effects of Treatment in Childhood Leukemia or Lymphoma* Facts*; Long-Term and Late Effects of Treatment in Adults* Facts*; Coping With Childhood Leukemia and Lymphoma;* and *Learning & Living With Cancer: Advocating for your child's educational needs*.

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 remission with leukemia-free survival—and probable cure. While adult cure rates lag behind the cure rates of children, adult remissions have increased over the last 10 years, and extended remissions are also more frequent.

Incidence, Causes and Risk Factors

Incidence. Approximately 5,960 new cases of acute lymphoblastic leukemia (ALL) are expected to be diagnosed in the United States in 2018. In 2014, there were an estimated 78,275 people either living with or in remission from ALL.

Acute lymphoblastic leukemia has an unusual age distribution. The incidence of ALL peaks between the ages of 1 and 4 years and then decreases until about age 45 years. The median age at diagnosis is 15 years, and about 52 percent of the patients diagnosed are younger than 20 years. See **Figure 4,** *below*.

Acute Lymphoblastic Leukemia (ALL): Age-Specific Incidence Rates 2011-2015

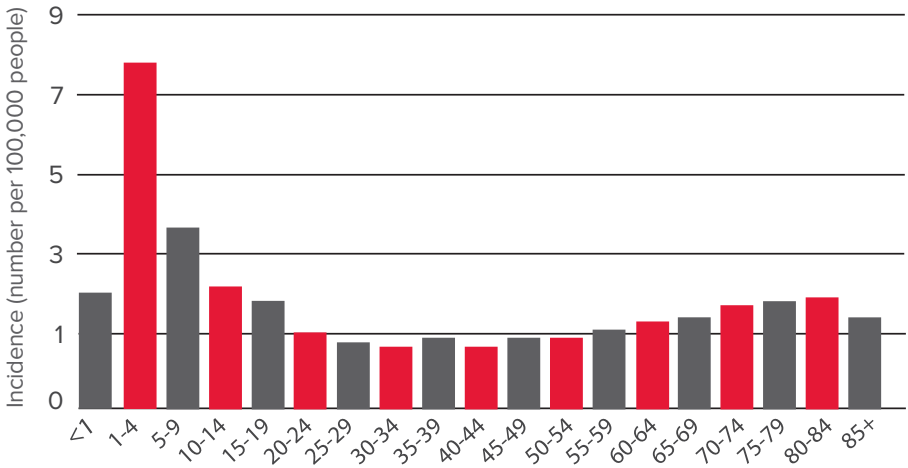

Figure 4. The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of acute lymphoblastic leukemia each year per 100,000 people, by age-group. Note that the risk of ALL is greatest in the first 5 years of life. An increase in occurrence is also seen in older individuals. Source: Surveillance, Epidemiology and End Results (SEER) Program; National Cancer Institute; 2017.

Causes and Risk Factors. In most cases, it is not clear what causes the genetic changes that lead to ALL. Researchers are trying to understand why these changes occur and how these changes develop into ALL. Not all patients with ALL have the same genetic mutations, and some genetic changes are more common than others. Usually DNA (deoxyribonucleic acid) mutations associated with ALL occur during a person's lifetime rather than being inherited from a parent.

There are some known risk factors for ALL. A "risk factor" is anything that increases a person's chance of developing a disease. Having a risk factor, however, does not mean that a person will develop the disease. Some people with several risk factors may never develop a disease, while others with no known risk factors may develop the disease. ALL is not contagious.

While the cause is unknown, several factors are associated with an increased risk of developing ALL, including

- Exposure to chemotherapy and radiation therapy. People who have had certain types of chemotherapy and radiation therapy may have an increased risk of developing ALL.
- Genetic disorders. Some genetic disorders, particularly Down syndrome, are associated with an increased risk of ALL. Although rare, other genetic conditions have been categorized as risk factors for ALL. These include neurofibromatosis, Klinefelter syndrome, Fanconi anemia, Shwachman-Diamond syndrome, Bloom syndrome and ataxia telangiectasia.
- Age. Children, adolescents or adults older than 70 years are at greater risk of developing ALL.
- Gender. Men are more likely to develop ALL than women.
- Race/ethnicity. In the United States, ALL is more common in Hispanics and whites.

Normal Blood and Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients to living cells and carries away the cells' waste products. It also contains immune cells to fight infections and platelets that can stop bleeding in damaged blood vessels. Blood is composed of plasma and cells.

Plasma. Plasma is largely made up of water in which many chemicals are dissolved. These chemicals each have a special role. They include

- Proteins
  - Albumin, the most common blood protein
  - Blood-clotting proteins (coagulation factors)made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
  - Immunoglobulins, proteins that help the body fight infection.
- Hormones, such as insulin and corticosteroids
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B_{12}
- Electrolytes, such as calcium, potassium and sodium.

Blood cells. There are three types of blood cells suspended in the plasma. They are

- Red blood cells (the cells that carry oxygen)
  - They make up a little less than half of the body's total blood volume.
  - They are filled with hemoglobin, which is a protein that picks up oxygen from the lungs and delivers it to the cells throughout the body. Hemoglobin then picks up carbon dioxide from the cells and delivers it to the lungs where it is removed when a person exhales.
- Platelets
  - Are fragments of cells (one-tenth the size of red blood cells)
  - Help stop bleeding from an injury. For example, when a person has a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of the blood vessel, clump together and plug up the bleeding site with the help of blood-clotting proteins, such as fibrin and electrolytes (eg, calcium).
- White blood cells (cells that fight infections). There are several types of white blood cells, including
  - Neutrophils. A type of immune cell that is a phagocyte (eating cell). It helps fight infection by ingesting microorganisms and releasing enzymes that kill the microorganisms. It is a type of granulocyte, a white blood cell that has small particles.
  - Eosinophils. A type of immune cell that has granules (small particles). It plays an important role in the body's response to allergic reactions and infection with parasites.
  - Basophils. A type of immune cell that has granules (small particles). It plays a role during allergic reactions and asthma.
  - Monocytes. A type of immune cell that is also a phagocyte. It can leave the bloodstream and enter tissues to attack invading organisms and fight off infection. It surrounds and kills microorganisms, ingests foreign material and removes dead cells.
  - Lymphocytes. This type of white blood cell is found mostly in the lymph nodes, spleen and lymphatic channels. It is a key part of the immune system. There are three major types of lymphocytes. They are
    - T lymphocytes (T cells)
    - B lymphocytes (B cells)
    - Natural killer (NK) cells.

New red blood cells, platelets and most white blood cells are formed in the bone marrow, a spongy tissue that is found in the central cavity of bones. The creation of new blood cells is controlled by the body's needs. The human body generates billions of new blood cells every day to replace old and worn out cells. Certain events also may prompt the body to produce additional blood cells. For example, the bone marrow will produce and release more white blood cells in response to an infection.

While red blood cells, white blood cells and platelets vary in appearance and function, they all originate from a single type of unspecialized cell called a "hematopoietic stem cell." Hematopoietic (blood-forming) stem cells are found in the bone marrow of the femurs (thigh bones), hips, vertebrae (back bones) and the ribs. An unspecialized hematopoietic stem cell can give rise to specialized cells that have specific functions. For example, a hematopoietic stem cell can become a red blood cell that carries oxygen throughout the body, or it can become a neutrophil, a white blood cell, that helps fight infections. The process by which an immature cell becomes a mature cell with specific functions is called differentiation."

The process of creating new blood cells through differentiation is called "hematopoiesis" (see **Figure 5** on *page 44*). When a stem cell divides, each "daughter" cell has the potential to either remain a stem cell or to become a specialized cell, such as a red blood cell, a white blood cell or a platelet. For those cells "committed" to specialize, the stem cell generates an intermediate cell. The intermediate cell is called a "precursor" or "progenitor" cell. While the stem cell remains in an immature, unspecialized state, the progenitor cell divides and undergoes multiple stages of development, becoming more specialized at each stage, until it becomes a particular type of mature blood cell.

The hematopoietic stem cell can give rise to lymphoid stem cells and myeloid stem cells. The lymphoid stem cells create lymphoid progenitor cells. Different types of progenitor or precursor cells develop into different types of mature blood cells. Through the process of differentiation, lymphoid progenitor or precursor cells mature into T cells, B cells or natural killer (NK) cells.

Myeloid stem cells create myeloid progenitor cells. These precursor or progenitor cells will develop into mature blood cells including red blood cells, platelets and certain types of white blood cells (eosinophils, basophils, neutrophils and monocytes.) For example, a myeloid progenitor cell will go through various stages of development to become a neutrophil: myeloid progenitor ➔ promyelocyte ➔ myelocyte ➔ metamyelocyte ➔ band ➔ neutrophil. In healthy people, stem cells in the bone marrow produce new blood cells continuously. Once the blood cells have matured, they leave the bone marrow and enter the bloodstream.

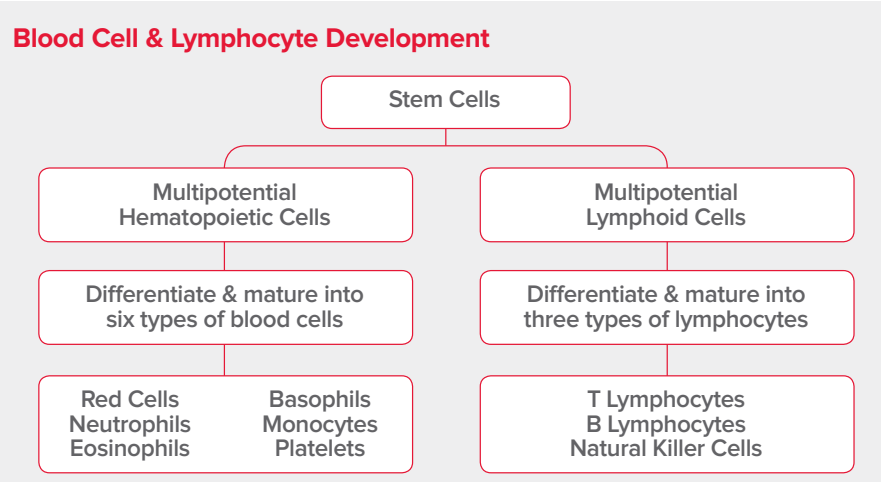

Figure 5. Stem cells develop into blood cells (hematopoiesis) and lymphocytic cells.

Resources and Information

LLS offers free information and services to patients and families affected by blood cancers. This section lists resources that can be helpful to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team members' knowledge and skills.

For Help and Information

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

- Call: (800) 955-4572 (Monday through Friday, from 9 am to 9 pm EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists
- Visit: www.LLS.org/InformationSpecialists.

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

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

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

Financial Assistance. LLS offers financial assistance to individuals with blood cancer. Visit www.LLS.org/finances for more information.

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

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

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultation provided by a registered dietitian who has experience in oncology nutrition. The dietitian will help you to devise healthy eating strategies that will work for you. A nutrition consultation also covers other issues; for example, the role of diet in side-effect management; survivorship nutrition, and how to cope with it; as well as information about how to access additional nutrition resources. For more information, please visit www.LLS.org/nutrition.

Podcast. Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. For more information and to subscribe, visit www.LLS.org/TheBloodline.

Continuing Education. LLS offers free continuing education programs for healthcare professionals. Please visit www.LLS.org/ProfessionalEd for more information.

Suggested Reading. A list of select books that are recommended for patients, caregivers, children and teens. To find out more, visit www.LLS.org/SuggestedReading.

Community Resources and Networking

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

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

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

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

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

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

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

Additional Help for Specific Populations

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

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

Children's Concerns. A family that has a child diagnosed with ALL is thrown into an unfamiliar world of treatment and follow-up care. The child, parents and siblings will all need support. Help is available. Do not 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 booklet *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

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

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

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

For more information, please

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

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

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

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

Health Terms

Alkylating Agent. A type of chemotherapy drug that is used in cancer treatment. It kills cancer cells by damaging the cells' DNA (deoxyribonucleic acid) which prevents the cells from dividing (reproducing).

Allogeneic Stem Cell Transplantation. A treatment that uses healthy donor stem cells to restore a patient's damaged or diseased bone marrow after high doses of chemotherapy and radiation. **See the free LLS booklet, *Blood and Marrow Stem Cell Transplantation*.**

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

Anthracyclines (Antitumor Antibiotics). A treatment for many types of cancer. Anthracyclines damage the DNA of cancer cells, causing them to die.

Antibody. A type of protein created by blood cells in response to an antigen (a substance that causes the body to mount a specific immune response). Antibodies help the body to fight against invaders that make a person sick. Antibodies can also be made in the laboratory and are used to help identify certain types of cancer and to help treat cancer.

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 in which stem cells are removed from a patient, stored and then returned to the patient after intensive treatment. **See the free LLS booklet, *Blood and Marrow Stem Cell Transplantation*.**

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

Biopsy. A procedure to remove cells or tissue from the body for examination by a pathologist. The pathologist may study the specimen under a microscope or perform other tests on the cells or tissue.

Blast Cell. An immature blood cell.

Blood Cell Count. See Complete Blood Count.

Blood Cells. There are three types of blood cells: red blood cells, which carry oxygen; white blood cells, which fight infections; and platelets, which help stop bleeding.

Bone Marrow. A spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. In adults, the bones of the hands, feet, legs and arms no longer contain blood-forming marrow—these bones are filled with fat cells. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried in the bloodstream throughout the body.

Bone Marrow Aspiration. A procedure that is part of a test that examines bone marrow cells to detect abnormal cells. A liquid bone marrow sample is usually taken from the patient's hip bone using a special needle. Usually this test is done at the same time as a bone marrow biopsy.

Bone Marrow Biopsy. A procedure that is part of 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 and tissue, 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 at the same time.

CBC. Complete blood count. See Blood Cell Count.

Central Line (Central Venous Catheter). A flexible tube used to deliver medications, fluids or blood products into the body or to withdraw blood samples from the body. See Port.

Central Nervous System (CNS) Prophylaxis. Treatment in which chemotherapy drugs are placed in the fluid that bathes the spinal cord and brain. In certain types of leukemia, particularly acute lymphocytic (lymphoblastic) leukemia and acute monocytic leukemia with high blood cell counts, the leukemic cells have a propensity to enter the covering of the spinal cord and brain.

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

Chimeric Antigen Receptor (CAR) T-Cell Therapy. A type of treatment that uses a patient's own T cells (a type of immune system cell). The T cells are taken from the blood and genetically modified so that they will attack cancer cells. The engineered T cells are now called CAR T cells. Large numbers of these engineered CAR T cells are grown in the laboratory and given to the patient by infusion.

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

Clinical Trial. A carefully planned and monitored research study that examines how well new medical approaches work in patients. The goal of clinical trials for blood cancers is to develop new treatments, improve quality of life and to increase survival time. A treatment that is proven safe and effective in a clinical trial is often approved by the United States Food and Drug Administration (FDA) for use as a standard treatment if it is either more effective or has fewer side effects than the current standard treatment.

Colony-Stimulating Factor. See Growth Factor.

Complete Blood Count (CBC). A laboratory test that measures the number of red blood cells, white blood cells and platelets in the blood. It also measures the amount of hemoglobin (the substance in the blood that carries oxygen) and the hematocrit (the amount of whole blood that is made up of red blood cells). Often called a "complete blood count" or "CBC."

Computed Tomography (CT) Scan. A procedure in which a series of x-ray images are linked to a computer to create 3-dimensional (3-D) views of tissues and organs in the body.

Conditioning Treatment. Intensive therapy used to prepare a patient for stem cell transplantation. Treatment may include chemotherapy and total body radiation.

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

Cycle of Treatment. A course of treatment followed by a period of rest to allow the body to recover. A cycle is the time between one round of treatment until the start of the next round of treatment. For example, chemotherapy given daily for 1 week followed by 3 weeks of rest is one cycle of treatment.

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

Cytotoxic Drug. Anticancer drug that kills cancer cells or prevents them from dividing. See Chemotherapy.

Differentiation. The process in which immature cells develop and mature into cells with specific functions. Stem cells either mature into red blood cells, platelets or white blood cells. See Hematopoiesis.

DNA. Deoxyribonucleic acid. The genetic matter found in all cells. It is passed to new cells during the process of cell division. A change or mutation in the DNA can lead to cell death, changes in the cell function, and in some cases, cancer.

DNA Repair Enzyme Inhibitor. A chemotherapy drug that makes the DNA (deoxyribonucleic acid) of cancer cells and tumors more susceptible to injury.

DNA Synthesis Inhibitor. A chemotherapy drug that reacts with DNA (deoxyribonucleic acid) to alter it chemically and keep it from permitting cell growth.

Echocardiogram. A computer picture of the heart created by bouncing sound waves (ultrasound) off internal tissues or organs of the chest. An echocardiogram shows the size, shape and position of the heart. It also shows parts inside the heart. An echocardiogram may be used to help diagnose heart problems.

Eosinophil. A white blood cell that participates in allergic reactions and helps fight certain parasitic infections. It promotes inflammation during allergic reactions and helps fight some parasitic infections.

Erythrocyte. See Red Blood Cell.

FDA. The abbreviation commonly used to denote the United States Food and Drug Administration. The FDA is responsible for assuring the safety, effectiveness and security of drugs, medical devices and the nation's food supply.

FISH. See Fluorescence In Situ Hybridization (FISH).

Flow Cytometry. A test that measures certain characteristics of cells in a sample including the size, shape, and the presence of tumor markers on the cell's surface.

Fluorescence In Situ Hybridization (FISH). A technique for studying abnormal chromosomes in cells and tissues. Pieces of DNA (deoxyribonucleic acid) that contain fluorescent molecules are added to cells or tissues on a slide. When the pieces of DNA bind to specific genes or chromosomes, they light up when viewed under a microscope. This test can be helpful in assessing risk and treatment needs and for monitoring treatment effectiveness.

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

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

Graft-Versus-Host Disease (GVHD). A disease that happens when cells from a donor (the graft) attack the tissues of the host (recipient). Most often GVHD attacks a patient's skin, liver and the stomach and gastrointestinal tract.

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

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

Hematologist. A doctor who specializes in treating blood cell diseases.

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

Hematopoiesis. The formation of all types of blood cells in the bone marrow. For the blood cell development process, see *Normal Blood and Bone Marrow* on *page 41*.

Hematopoietic Stem Cell. An immature cell that can develop into any type of blood cell including red blood cells, white blood cells and platelets.

Hemoglobin. The iron-containing substance in red blood cells that carries oxygen around the body. Hemoglobin concentration decreases when there is a reduction in the number of red blood cells. This condition 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. Human leukocyte antigen factors are inherited from an individual’s 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. 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.

Hyperdiploidy. In humans, having more than the normal 46 chromosomes.

Hypodiploidy. In humans, having less than the normal 46 chromosomes.

Immune System. A complex network of cells, tissues and organs that work together to defend the body against infections.

Immunophenotyping. A process that uses antibodies to find specific types of cells based on the types of antigens or markers on the surface of the cells.

Immunotherapy. The term for several treatment approaches used by doctors to harness the body’s immune system to treat leukemia and other diseases. These therapies include monoclonal antibody therapy, radioimmunotherapy and vaccine therapy.

Monoclonal antibodies are proteins made in the laboratory that either react with or attach to antigens on the target cells. The antibodies are used therapeutically in three ways: as “naked” antibodies (monoclonal antibodies), as antibodies to which radioactive isotopes are attached (radioimmunotherapy), and as antibodies to which toxins are attached (immunotoxins). **For more information, see the free LLS booklet *Immunotherapy* Facts.**

Intrathecal. The designation for the fluid-filled space between the thin layers of tissue that cover the brain and the spinal cord. This lining is called the "meninges." In some situations (when leukemia cells are in the meninges), drugs are administered directly into the spinal canal. This treatment is called "intrathecal therapy."

Karyotype. An organized profile of a person's chromosomes. It exhibits the size, shape and number of chromosomes in a sample of cells.

Late Effect. A medical problem that either does not appear or is not noticed until years after treatment ends. Treatment-related cancer and heart disease are examples of late effects.

Leukocyte. See White Blood Cell.

Lumbar Puncture. A procedure in which a thin needle is put into the spinal column to collect spinal fluid or to administer anticancer drugs to the central nervous system (CNS). Another term for lumbar puncture is "spinal tap."

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

Lymphocyte. A type of white blood cell that is important to the body's immune system. There are three major types of lymphocytes: B lymphocytes, which produce antibodies to help combat infections; T lymphocytes, which have several functions, including assisting B lymphocytes in making antibodies; and natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Lymphoid. Referring to lymphocytes (white blood cells).

Macrophage. A type of white blood cell that surrounds and kills microorganisms, eats dead cells and helps lymphocytes with their immunity functions.

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

Marrow. See Bone Marrow.

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

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

Monoclonal Antibody. A type of synthetic protein that can bind to substances in the body including cancer cells. Monoclonal antibodies are used in cancer treatment and are used to target 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.

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 bloodstream and enters the tissue, it becomes a macrophage.

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

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

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

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

Palpate. To examine by touch.

Pathologist. A doctor who has special training in identifying diseases by studying cells and tissues under a microscope.

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

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

Petechiae. Pinhead-sized red spots under the skin caused by bleeding. Petechiae may be a sign of a low platelet count.

Phagocyte. A type of white blood cell that protects the body from infection by eating and killing microorganisms such as bacteria and fungi. Neutrophils and monocytes are the two main types of these phagocytes. Once an infection occurs, phagocytes migrate from the bloodstream and enter the infected tissue.

Philadelphia Chromosome (Ph Chromosome). It is formed when parts of chromosomes 9 and 22 break off and trade places. The result is a chromosome 22 that is shorter than normal. The exchange of DNA (deoxyribonucleic acid) between chromosomes 9 and 22 results in the creation of a new fusion gene called *"BCR-ABL"* on chromosome 22.

Ph-like. Philadelphia chromosome (Ph)-like acute lymphoblastic leukemia (ALL) is a high-risk subtype of ALL in children.

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

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

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 used to expand trace amounts of DNA (deoxyribonucleic acid) so that the specific type of the DNA can be studied. This technique has become useful in detecting a very low concentration of residual blood cancer cells, too few to be seen using a microscope. This test can detect the presence of one blood cancer cell among 500,000 to 1,000,000 healthy blood cells.

Port. A small device used to facilitate access to a central line for blood draws and to administer treatments such as intravenous fluids, drugs and blood transfusions. The port is placed under the skin, usually in the chest. It is attached to a catheter (a thin, flexible tube) that is threaded into a large vein.

Protocol. A plan for medical treatment.

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 Cell. A red blood cell contains hemoglobin. It carries oxygen to the tissues of the body. Red blood cells make up about 40 to 45 percent of blood volume in healthy people. Red blood cells are also called “erythrocytes.”

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

Regimen. A treatment plan that specifies the dosage, the schedule, and the duration of treatment.

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

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

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

Risk Factor. A factor, scientifically established, that increases 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 the DNA’s (deoxyribonucleic acid) instructions for making proteins.

Spinal Tap. See Lumbar Puncture.

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

Stem Cell. A cell from which other types of cells develop. For example, blood cells such as red blood cells, white blood cells and platelets develop from blood-forming stem cells. See Hematopoiesis.

Stem Cell Transplantation. See Allogeneic Stem Cell Transplantation, Autologous Stem Cell Transplantation and Reduced-Intensity Stem Cell Transplantation.

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

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. A genetic abnormality in which a piece of one chromosome breaks off and attaches to another chromosome. Sometimes genetic material is exchanged between two different chromosomes. When a translocation takes place, the gene at which the break occurs is altered. See Mutation.

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

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

World Health Organization (WHO). An agency of the United Nations that deals with major health issues around the world. The World Health Organization sets standards for health care and medicines and publishes scientific papers and reports.

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