LEUKEMIA & LYMPHOMA SOCIETY®

PROVIDING THE LATEST INFORMATION FOR PATIENTS & CAREGIVERS

Acute Lymphoblastic Leukemia (ALL) in Adults

Revised **2020**

Support for this publication provided by Takeda | ONCOLOGY

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.

Discover what thousands already have at **www.LLS.org/Community**

Join our online social network for people who are living with or supporting someone who has a blood cancer. Members will find

- **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

Acknowledgement

The Leukemia & Lymphoma Society appreciates the review of this material by

Ryan D. Cassaday, MD
Attending Physician, Hematological Malignancies Program
Seattle Cancer Care Alliance
Associate Professor, Division of Hematology
University of Washington School of Medicine
Associate Professor, Clinical Research Division
Fred Hutchinson Cancer Research Center
Seattle, WA

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Introduction

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

People can develop ALL at any age from infants to the very elderly. While most cases of ALL are diagnosed in patients younger than age 20, most deaths from ALL occur in adults.

This booklet focuses on ALL in adults, but it also includes information on young adults. For more information about ALL in children, visit **www.LLS.org/booklets to see the free LLS book, *Acute Lymphoblastic Leukemia (ALL) in Children and Teens***.

Over the past several decades, advances in ALL testing and treatment have resulted in improved remission rates for adults. Despite higher remission rates, relapses still commonly occur. More work remains to be done, and researchers are studying new therapies in clinical trials for adult patients with ALL.

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 for the disease and lists new treatment options being researched in clinical trials. It also 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 about ALL or that it reinforces what you already know. We hope that you will keep this booklet handy and, should you ever feel alone when confronting problems, you will turn to it for information and guidance to locate the support and resources you need.

We are here to help.

All LLS publications mentioned in this booklet are free and can be viewed, downloaded or ordered online at www.LLS.org/booklets.

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Leukemia

Leukemia is a cancer of the blood and bone marrow. Bone marrow is the sponge-like tissue in the center of most bones, where blood cells form. Leukemia

begins in one of the immature cells in the bone marrow. One or more changes (mutations) occur in the DNA of the cell, and it becomes a type of cancer cell, called a "leukemia cell."

Leukemia cells do not mature into healthy, functioning blood cells. They grow more 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. These cells spill out of the bone marrow into the bloodstream and may then spread into organs such as the liver and spleen.

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 (meaning how quickly the disease gets worse) is one of the factors that 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. Blood stem cells develop into two primary types: lymphoid and myeloid. As lymphoid stem cells (or "lymphoblasts") mature, they become a type of white blood cell called "lymphocytes." The two major types of lymphocytes are B cells and T cells. Myeloid stem cells eventually become red blood cells, platelets or certain types of white blood cells (other than lymphocytes). Leukemia is called "lymphoblastic" or "lymphocytic" if the cancerous change begins in a lymphoid cell. Leukemia is called "myeloid" or "myelogenous" if the cancerous cell change starts in an early form of a myeloid cell.

This booklet focuses on ALL, but there are other cancers, called "lymphomas," that also begin in lymphoid cells. Most lymphomas arise from more mature lymphoid cells, but in rare instances they can develop from lymphoblasts. 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 the blood. In contrast, lymphomas are mostly located in lymph nodes or other lymphatic tissues or organs. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens rather than traditional lymphoma therapy. Therefore, if you have been diagnosed with lymphoblastic lymphoma, this book may also be helpful to you.

For general information about ALL, visit www.LLS.org/booklets to see the free LLS booklet *The ALL Guide: Information for Patients and Caregivers*.

Acute Lymphoblastic Leukemia

How Acute Lymphoblastic Leukemia (ALL) Develops. There are three main types of blood cells: red blood cells, white blood cells and platelets. Red blood cells carry oxygen throughout the body. White blood cells help fight infections. Platelets help stop bleeding by clumping together (clotting) at the site of an injury.

Blood cells begin as hematopoietic stem cells in the bone marrow. Hematopoietic stem cells are immature (undeveloped) blood cells. In healthy bone marrow, these blood-forming stem cells eventually develop into red blood cells, white blood cells and platelets through a process called "differentiation."

In people with ALL, a mutation or a series of mutations in the DNA (genetic material) of a lymphoid stem cell (or "lymphoblast") result in the formation of leukemia cells, which are immature cells stuck in the earliest stages of cell development. These leukemia cells, also referred to as "ALL blasts," cannot mature into fully functioning white blood cells.

Genetic errors in the mutated cell cause the cell to keep growing and dividing, whereas 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 the leukemia cells multiply uncontrollably and quickly accumulate in the bone marrow, they slow down or stop the production of normal, healthy red blood cells, white blood cells and platelets. As a result, there are too many immature, leukemic blast cells that cannot fight infections and too few mature, functional red and white blood cells and platelets.

By the time ALL is diagnosed, the number of healthy red blood cells, white blood cells and platelets is usually lower than normal. Having low levels of normal cells may result in infections, anemia, and excessive bleeding or bruising.

Medical term:	Description:
Anemia	Low red blood cell count
Thrombocytopenia	Low platelet count ("thrombocyte" is another word for platelet)
Neutropenia	Low neutrophil count (a neutrophil is a type of white blood cell)

Signs and Symptoms

Signs and symptoms are changes in the body that may indicate the presence of disease. A sign is a change that the doctor sees during an exam or in 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 referred to a specialist called a hematologist-oncologist. This is a doctor who has special training in diagnosing and treating blood disorders and blood cancers, such as leukemia, lymphoma and myeloma.

It is common for someone with ALL to feel a loss of well-being because of the lack of normal, healthy blood cells. This happens when the leukemia cells in the bone marrow crowd out the normal blood-making cells. Consequently, patients with ALL may not have enough mature red blood cells, white blood cells and/or platelets, and often have symptoms related to low blood cell counts.

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
- Heavier or more frequent menstrual periods in females

Other general symptoms of ALL include:

- Night sweats
- Pain in bones or joints
- Enlarged spleen, liver or lymph nodes

- Abdominal pain
- Pain or feeling of fullness below the ribs
- Unexplained weight loss or loss of appetite
- Wheezing, coughing or painful breathing

The symptoms of ALL may be similar to those of other blood disorders or medical conditions. Speak with your doctor if you have any of these symptoms to ensure proper diagnosis and treatment.

Diagnostic Testing

While certain signs and symptoms may indicate that a person has ALL, laboratory tests are needed to confirm the diagnosis. It is important to have an accurate diagnosis, as it helps the doctor to:

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

Talk to your doctor about

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

Some of these tests may be repeated both during and after treatment to evaluate its effectiveness.

Medical History. 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 your blood relatives.

Physical Examination. The doctor will want to know about your current symptoms and will conduct a physical examination. During the examination, the doctor may listen to your lungs and heart and carefully examine your body for signs of infection and disease. To check the internal organs, the doctor may also feel different parts of your body. For example, the doctor may feel the abdomen to see if you have an enlarged liver or spleen. Because ALL can cause enlarged lymph nodes, the doctor may check the lymph nodes in your neck and armpits. In men, the doctor may also examine the testicles to see if there are any masses.

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 also measures the amount of hemoglobin in the red blood cells. The CBC should include a differential, which measures the numbers of the different types of white blood cells in the sample.

People with ALL often have a high number of white blood cells, but most of these are leukemia cells that do not protect against infection. Meanwhile, they do not have enough mature white blood cells and may also have a low number of red blood cells and platelets.

If the CBC findings suggest leukemia, a diagnosis of ALL can sometimes be confirmed with additional testing of the blood sample. Sometimes, however, an ALL diagnosis can be made only after the examination of a sample of bone marrow cells. Less often, an ALL diagnosis is made after a biopsy of a lymph node mass. A lymph node biopsy is typically done to diagnose lymphoblastic lymphoma. Patients with enlarged lymph nodes may undergo both lymph node and bone marrow testing in order to correctly diagnose lymphoblastic lymphoma or lymphoblastic leukemia. For more information on lymphoblastic lymphoma, see page 12.

Bone Marrow Aspiration and Biopsy. These are two procedures that remove bone marrow cells and test them for abnormalities. They are generally done at the same time, either at the doctor's office or in a hospital.

The samples are usually taken from the patient's pelvis or "hip bone," after medicine has been given to numb the skin and surface of the bone. 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 wider needle is used to remove a sample of solid bone that contains bone marrow. Both samples are sent to the lab where they are examined under a microscope. See **Figure 1** on page 8.

Figure 1. How are the Blood and Bone Marrow Tests Done?

Blood Test. A small amount of blood is taken from the patient's arm with a needle. The blood is collected in tubes and sent to a lab for testing.

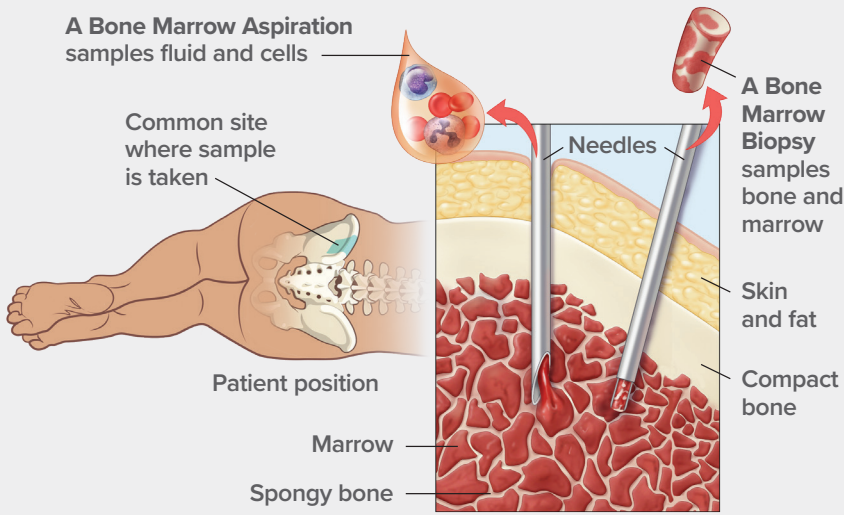
Bone Marrow Aspiration. A sample of fluid with cells is removed from the bone marrow and sent to a lab for testing.

Bone Marrow Biopsy. A very small amount of bone filled with marrow cells is taken from the body and sent to a lab for testing.

Both bone marrow tests are done with special needles. Some patients are awake for the procedue. They get medication first to numb the part of the body that will be used to get the sample of cells. Some patients are given a drug that makes them sleep during this procedure. The sample of cells is usually taken from the patient's hip bone.

Blood and marrow tests may be done in the doctor's office or in a hospital. A bone marrow aspiration and biopsy are almost always done at the same visit. Blood and bone marrow tests may be done both during and after treatment. The tests are respeated to see if treatment is working.

Bone Marrow Aspiration and Biopsy



Left: The place on the back of the patient's pelvic bone where a bone marrow aspiration or biopsy is done. **Right:** Where the needle goes inside the bone to collect the liquid sample for aspiration and the bone sample for biopsy. The needles are different sizes for each of these tests.

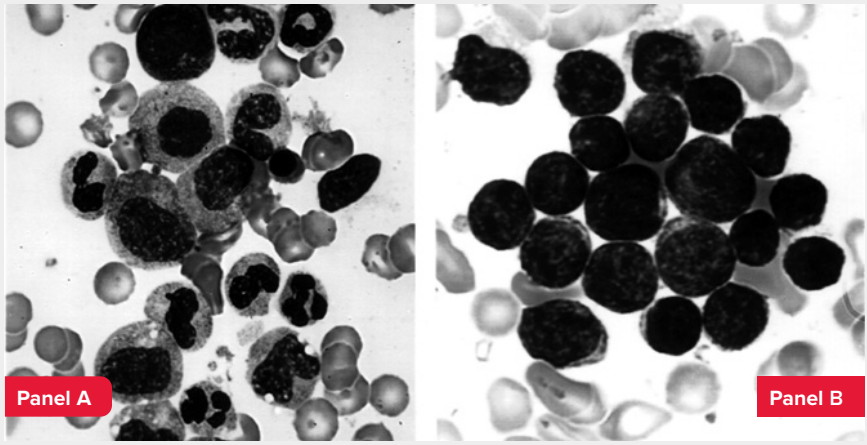
Cell Assessment. At the laboratory, a hematopathologist examines the blood and bone marrow samples. A hematopathologist is a doctor who has special training in identifying blood diseases by studying cells under a microscope.

The hematopathologist examines the blood and bone marrow cells under a microscope to determine their size, shape and type, and to identify other cell features. Whether the cells look like normal, mature blood cells or abnormal, immature blood cells (blast cells) is an important finding. See **Figure 2** below.

The percentage of blast cells identified in the samples is another important finding. 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.

A diagnosis of ALL generally requires at least 20 percent of the cells in the bone marrow to be blasts. Although, in most people diagnosed with ALL, the level of blast cells in the bone marrow is well over 20 percent, a higher percentage of blast cells in the bone marrow does not necessarily mean a poorer prognosis.

Figure 2. Acute Lymphoblastic Leukemia (ALL) Cells



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.

If leukemia is found, additional tests are done on the blood and bone marrow samples to gather information about the type and subtype of ALL.

Flow Cytometry. This laboratory test can detect specific types of cancer cells based on the antigens or proteins on the surface of the cells. The pattern of the surface proteins is called the “immunophenotype.” It is used to help diagnose specific types of leukemia and lymphoma cells.

A bone marrow sample is often used for this test, but it can also be done with a blood sample. The sample of cells is treated with special antibodies, created in a laboratory, that only bind to cells that have a specific antigen on them. The cells are then passed through a laser beam.

Depending on the type of leukemia, the leukemia cells can have different antigens on their surfaces. Certain antigens, called "cluster of differentiation (CD) proteins," are helpful in identifying leukemia cells.

Flow cytometry helps to confirm an ALL diagnosis. It is also used to determine the type of lymphocytes (B cells or T cells) in which the disease 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 examine the chromosomes and genes in a patient's leukemia cells.

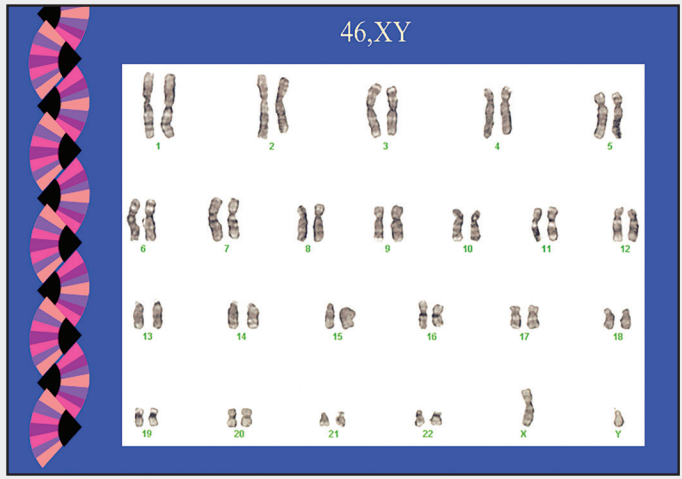
Cytogenetic Analysis (Karyotyping). In this test, a hematopathologist or other type of specialist uses a microscope to examine the chromosomes inside cells. In patients with ALL, karyotyping is used to look for abnormal changes in the chromosomes of leukemia cells.

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; these changes include, for example, 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 trade places. A translocation may result in a "fusion gene," an abnormal gene that is formed when two different genes are fused together.

Cytogenetic testing can be done with either a bone marrow sample or a blood sample. The leukemia cells in the sample are allowed to grow in the laboratory and then are stained prior to examination. The stained sample is examined under a microscope and then photographed to show the arrangement of the chromosomes (called a karyotype). The karyotype shows if there are any abnormal changes in the size, shape, structure or number of chromosomes in the leukemia cells. See **Figure 3** on page 11.

Cytogenetic analysis provides important information for determining a patient's treatment options and prognosis. This information can predict how the disease will respond to treatment. 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.

Figure 3. Normal Male Karyotype



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

Fluorescence in Situ Hybridization (FISH). This cytogenetic technique is a lab test used to identify and examine specific genes or chromosome regions in cells. In cases of ALL, doctors use FISH to detect certain abnormal changes in the chromosomes within leukemia cells, including translocations. Pieces of DNA that contain special fluorescent dyes are created 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 fluorescence microscope. Many abnormal changes can be seen with a standard microscope, but FISH testing can also detect changes that are too small to be seen in more basic cytogenetic tests.

Polymerase Chain Reaction (PCR). This is a very sensitive lab test used to detect and measure certain genetic mutations and chromosomal changes that are too small to be seen with a microscope. PCR essentially increases or "amplifies" small amounts of specific pieces of either RNA (ribonucleic acid) or DNA (deoxyribonucleic acid) to make them easier to detect and measure. This test can find a single leukemia cell among more than 500,000 to 1,000,000 normal cells. PCR testing is one method used to determine the amount of minimal residual disease (MRD) in patients, which refers to the small amount of cancer cells that may remain in the body after treatment. This test can be done with either a bone marrow sample or a blood sample.

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

Diagnosis and Cell Classification

The diagnosis of 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 on the patient's lab test results.

Subtypes of ALL. The subtypes of ALL are based on certain features of the leukemia cells. Determination of the ALL subtype is an important factor in treatment planning. Based on a patient's ALL subtype, the doctor will decide which drugs, drug combinations and drug dosages are indicated and will determine the appropriate duration of treatment.

Immunophenotyping. Leukemia cells can be classified by antigens found on their surface, known as "immunophenotypes." The World Health Organization (WHO) classifies ALL based on the immunophenotype of the leukemia cell in the following ways (see **Table 1** on page 13):

- B-cell lymphoblastic leukemia or lymphoma. This subtype begins in immature cells that would normally develop into B cells. If the bone marrow has 20 percent or more lymphoblasts, the disease is called B-cell lymphoblastic leukemia (B-cell ALL). If the lymphoblasts are restricted to a mass in a lymph node or other lymph tissue and less than 20 percent of the bone marrow cells are lymphoblasts, it is called B-cell lymphoblastic lymphoma. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens rather than traditional lymphoma therapy.

  B-cell ALL is the most common ALL subtype, accounting for 75 percent of adult cases of ALL. Within the B-cell lineage, the cell surface markers (proteins) differ according to the stage of cell maturation.

  Before 2008, the WHO classified B-cell lymphoblastic leukemia as "precursor B-lymphoblastic leukemia." This older term is sometimes 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 unique in that it can resemble treatment used for both ALL and non-Hodgkin lymphoma. **For more information on Burkitt leukemia, see the free LLS booklet *Non-Hodgkin Lymphoma*.**

- T-cell lymphoblastic leukemia or lymphoma. This subtype begins in immature cells that would normally develop into T cells. If 20 percent or more of the bone marrow cells are lymphoblasts, the disease is called T-cell lymphoblastic leukemia (T-cell ALL). If the lymphoblasts are restricted to a mass in a lymph node or other lymph tissue and less than 20 percent of the bone marrow cells are lymphoblasts, it is called T-cell lymphoblastic lymphoma.

  T-cell ALL is less common than B-cell ALL, accounting for about 25 percent of adult ALL cases.

Table 1. 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

Source: Classification of acute lymphoblastic leukemia types created by the World Health Organization (WHO).

Genetic Changes. In addition to classifying ALL as either B-cell or T-cell, it is further classified based on certain changes to the chromosomes and genes found in the leukemia cells (see **Table 2** below). This identification of specific genetic 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 from one chromosome breaks off and becomes attached to a different chromosome. Sometimes pieces from two different chromosomes trade places. A translocation may result in a "fusion gene," an abnormal gene that is formed when two different genes are fused together.

Another type of genetic change that occurs in ALL is the result of numerical abnormalities. A numerical abnormality is either a gain or loss in the number of chromosomes from the normal 46 chromosomes. A change in the number of chromosomes can affect the growth, development and functioning of body systems.

About 75 percent of adult ALL cases can be classified into subgroups based on chromosomal abnormalities and genetic mutations. Not all patients have the same genetic changes. Some changes are more common than others, and some have a greater effect on a patient's prognosis.

See the free LLS booklet *Understanding Genetics* for more information about genetics and genetic testing.

Table 2. Common Chromosomal and Molecular Abnormalities in ALL

Cytogenetics	Gene(s) Associated	Frequency in Adults
Hyperdiploidy (>50 chromosomes)	—	7%
Hypodiploidy (<44 chromosomes)	—	2%
t(9;22)(q34;q11): Philadelphia chromosome (Ph)	*BCR-ABL1*	25%
t(12;21)(p13;q22)	*ETV6-RUNX1 (TEL-AML1)*	2%
t(v;11q23) [eg, t(4;11) and others], t(11;19)	*KMT2A rearranged*	10%
t(1;19)(q23;p13)	*TCF3-PBX1 (E2A-PBX1)*	3%
t(5;14)(q31;q32)	*IL3-IGH*	< 1%
t(8;14), t(2;8), t(8;22)	*c-MYC*	4%
t(1;14)(p32;q11)	*TAL-1*[a]	12%
t(10;14)(q24;q11)	*HOX11 (TLX1)*[a]	8%

Cytogenetics	Gene(s) Associated	Frequency in Adults
t(5;14)(q35;q32)	*HOX11L2*[a]	1%
t(11;14)(q11)[eg, (p13;q11), (p15;q11)]	*TCRα* and *TCRσ*	20-25%
BCR-ABL1-like/Ph-like	various	10-30%
B-ALL with *iAMP21*	*RUNX1*	—
ETP	various	2%
Ikaros	*IKZF1*	25-35%

[a]Abnormalities observed exclusively in T-cell ALL; all others occur exclusively or predominantly in B-cell ALL.

Abbreviations: t, a translocation between chromosomes; q, the long arm of a chromosome (the lower half); inv, an inversion in a chromosome; p, the short arm of a chromosome (the upper half).

Adapted from NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia. 2020.

Treatment Planning

Pre-Treatment Testing. Before you start treatment, your doctor will perform tests to learn more about your overall health and your leukemia, including determining whether the leukemia has spread to other parts of the body. Doctors use this information for treatment planning. Some of these tests are summarized below.

Blood Tests. The following are blood tests used for treatment planning.

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 also measures the amount of hemoglobin in the red blood cells. The CBC should include a differential, which measures the numbers of the different types of white blood cells in the sample.

Blood Chemistry Profile. This blood test 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 (blood sugar), uric acid and enzymes. Blood chemistry test findings indicate how well a person's kidneys, liver and other organs are working. Although this test is not used to diagnose leukemia, if the results show that there is an abnormal amount of a particular substance in the blood, it 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 cancer treatments.

Liver Function Tests. The liver is the largest organ inside the body. It is located in the upper right side of the abdomen. It helps the body digest food, store energy and remove toxins from the blood. If leukemia cells are present in the liver, they can affect liver function. Also, some chemotherapy drugs can damage the liver and affect liver function. Liver function tests are done to check how well the liver is working.

Coagulation Tests. These tests measure the blood's ability to clot and stop injuries from bleeding. Certain proteins, called coagulation factors, are needed for clotting. These proteins are made by the liver. In addition to checking how well the blood is able to clot, these tests can determine whether there are deficiencies in some proteins, such as fibrinogen. A coagulation test can help the doctor determine if your blood is clotting properly.

TLS Panel. Patients with ALL may be at high risk for developing a condition called "tumor lysis syndrome" (TLS). This condition can occur when a large number of cancer cells die within a short period of time. As the leukemia cells die, they break apart and release their contents into the bloodstream, which changes the normal balance of chemicals in the blood. This can overwhelm the kidneys because they cannot get rid of these substances all at once. The effects of TLS can be life-threatening; they can be severe at the time of initial leukemia diagnosis and during the early phases of treatment, especially if white blood cell counts are very high before induction therapy. A TLS panel can help your doctor assess if you are likely to get TLS or if you already have it.

HLA Typing. This consists of a blood test to identify certain proteins, called human leukocyte antigens (HLAs), found on the surface of most cells in the body. These proteins make up a person's tissue type, which varies from person to person. They also play an important role in the body's immune response to foreign substances by helping the body distinguish its own cells from foreign cells. HLA typing is done before allogeneic stem cell transplantation to find out if there is a tissue match between the donor and the person receiving the transplant. Although HLA typing is not used to diagnose leukemia, it is an important test for newly diagnosed ALL patients, if allogeneic stem cell transplantation is being considered as a treatment option. For more information on stem cell transplantation, see page 30.

Lumbar Puncture. ALL can spread to the cerebrospinal fluid, the fluid that flows around the brain and spinal cord. In order to determine whether leukemia cells have spread to this area, a sample of the cerebrospinal fluid is tested.

The procedure used to collect the cerebrospinal fluid from the spinal column is called a lumbar puncture or spinal tap. 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 cerebrospinal fluid. 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 (pictures) of the inside of the body. A radiologist is a doctor who specializes in reading these images. Various types of imaging tests are used to detect where a cancer is located in the body.

Computed Tomography (CT) Scan. In this type of imaging test, a computer linked to an x-ray machine is used to take a series of detailed pictures of areas inside the body. In some cases, leukemia may grow outside the bone marrow—most commonly in lymph nodes. A CT scan may be used to see whether leukemia cells are accumulating in lymph nodes in the chest or abdomen, or in organs such as the spleen or liver.

Positron Emission Tomography (PET) Scan. For this type of imaging test, a small amount of radioactive glucose (sugar) is injected into a patient's vein. A PET scanner is a large, doughnut-shaped machine with a round hole in the middle, similar to a CT scanner. The PET scanner detects areas in the body where large amounts of glucose are being used. In the images, the cancer cells appear brighter than the normal cells because they use sugar more quickly than normal cells. A PET scan may be used to see if there are cancer cells in the lymph nodes or organs.

Positron Emission Tomography-Computed Tomography (PET-CT) Scan. This procedure combines images from both a PET scan and a CT scan. The combined scans give a more detailed image of areas inside the body than either scan can by itself.

Magnetic Resonance Imaging (MRI) Scan. This imaging test uses magnetic fields and radio waves to create images of the body's organs and tissues, as well as 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 headaches or seizures that suggest that ALL cells may have spread to the brain and spinal cord.

Ultrasound. This imaging test uses high-energy sound waves to examine tissues and organs inside the body. For example, it can detect cancer in a man's testicles. If the testicles are not the same size or have any lumps, the doctor may order an ultrasound to see whether there is a mass in the testicles.

Echocardiogram. Since some cancer treatments can damage the heart, your doctor may do this test as part of the treatment planning process to check how well your heart pumps blood. A computerized image of the heart is created by bouncing ultrasound waves off internal tissues or organs in the chest. An echocardiogram shows the heart's size, shape and position, as well as its internal structures. It also shows if the heart is beating and pumping blood normally.

See the free LLS booklet *Understanding Lab and Imaging Tests* for more information about these tests. To view interactive 3D illustrations of some lab and imaging tests, visit www.LLS.org/3D.

Prognostic Factors. Certain factors can affect a patient's prognosis—the chance of recovery or cure. These are called "prognostic factors." Doctors use prognostic factors to help predict how a patient's disease is likely to respond to treatment. These factors help doctors plan the most appropriate initial treatment regimen for each patient. In addition, they help to determine whether or not stem cell transplantation should be considered as a treatment option for the patient, and if so, when to perform the transplant.

The prognostic factors for adults with ALL are summarized below.

- 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 a lower white blood cell count (less than 30,000/µL for B-cell ALL and less than 100,000/µL for T-cell ALL) at the time of diagnosis generally have a better prognosis.
- Gene or chromosome abnormalities: Certain changes in the chromosomes or genes of leukemia cells can make the disease either easier or harder to treat. See **Table 3**, below.
- Response to induction therapy: Patients who have a better response to their initial therapy, called "induction therapy," typically have a lower risk of relapse.

Table 3. Cytogenetic Risk Groups for B-Cell ALL

Risk Groups	Cytogenetics
Good risk	• Hyperdiploidy (51-65 chromosomes) ◦ Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome • t(12;21)(p13;q22): *ETV6-RUNX1*
Poor risk	• Hypodiploidy (<44 chromosomes) • *KMT2A* rearranged (t[4;11] or others) • t(v;14q32)/IgH • 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; intrachromosomal amplification of chromosome 21 (*iAMP21*)

Abbreviations: ALL, acute lymphoblastic leukemia; Ph-like, Philadelphia-like; TKI, tyrosine kinase inhibitor.
Source: The National Comprehensive Cancer Network (NCCN) Acute Lymphoblastic Leukemia Guidelines. 2020.

Fertility. Some cancer treatments can affect your fertility (the ability to have children in the future). Before you begin your cancer treatment, it is important to talk with your doctor about whether your treatment could affect your fertility. You may also want to speak with a fertility specialist. A fertility specialist is a doctor who diagnoses and treats problems related to infertility. The fertility specialist can talk to you about possible options for preserving your fertility.

You may be able to take steps before treatment begins to preserve your fertility. However, delaying treatment to address fertility options may not always be recommended. You may need to start treatment right away.

For more information about fertility preservation, see the free LLS booklet *Fertility Facts*.

Choosing a Hospital and Doctor. A diagnosis of ALL is associated with a wide range of outcomes, so it is essential to seek treatment in a center with hematologist-oncologists who are experienced in the care of patients who have ALL. A hematologist is a doctor who has special training in disorders of the blood, and an oncologist is a doctor who has special training in cancer. A hematologist-oncologist specializes in treating blood cancers.

Typically, ALL patients need to start treatment as soon as possible after diagnosis. If time allows, however, you may want to seek a second opinion from another doctor. A second opinion may help you feel more confident about the recommended treatment plan. The second opinion should come from another hematologist-oncologist, preferably one who treats ALL. This type of doctor will usually have the most knowledge and experience about the latest ALL treatment options.

If you are unsure about getting a second opinion, or feel uncomfortable about how to tell a doctor you are seeking a second opinion, call our Information Specialists to discuss a way to do so that makes you feel comfortable. You may also want to check with your insurance company to be sure that your policy covers the cost of getting a second opinion.

Treatment Options

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

Before you begin treatment, you and your doctor will discuss your treatment options. One option may be a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all of your treatment options, including clinical trials, you will be taking an active role in a very important decision that affects you.

Talk to your doctor about

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

Treatment Overview. Treatment for ALL typically consists of long-term multidrug chemotherapy given in three phases: induction, consolidation and maintenance. See **Figure 4** on page 26. 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. See **Table 4** on page 23.

Induction. The first phase of treatment is called "induction." The goal of induction is to destroy as many cancer cells as possible in order to achieve (induce) a remission. This means that leukemia cells are no longer found in bone marrow samples, and blood counts become normal. Induction therapy often lasts about 4 weeks.

Chemotherapy 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 **pegaspargase** and/or **cyclophosphamide**. For more information on chemotherapy, see page 27.

For patients with Philadelphia chromosome-positive (Ph+ ALL), a tyrosine kinase inhibitor (TKI) such as **imatinib** or **dasatinib** is often included as well. For more information on TKIs, see page 27.

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

Central Nervous System (CNS) Prophylaxis and Treatment. It is uncommon for leukemia cells to be present in the cerebrospinal fluid at the time of diagnosis, occurring in only 3 to 7 percent of cases. However, without the routine administration of a therapy targeting the central nervous system (referred to as "CNS prophylaxis"), leukemia cells eventually spread to the cerebrospinal fluid in a large percentage of patients (50 percent or more). CNS prophylaxis is administered to prevent leukemia cells from spreading to the area around the brain and the spinal cord. It is typically given to all patients during the induction phase, the consolidation phase and, in some cases, the maintenance phase.

Central nervous system-directed therapy may include:

- Intrathecal chemotherapy, in which 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**).
- Systemic chemotherapy, in which anticancer drugs are given through a vein to reach any leukemia cells in the central nervous system. These drugs may include **high-dose methotrexate**, **intermediate-/high-dose cytarabine** and **pegaspargase**.
- Cranial irradiation, in which radiation therapy to the brain is used to kill cancer cells.

Assessing Treatment Response. At the end of induction therapy, blood and bone marrow tests will be done to see how well your treatment is working. The doctor will check to see whether you have achieved a complete remission. A complete remission is achieved when:

- No more than 5 percent of cells in the bone marrow are blast cells
- Blood cell counts are back to normal
- All signs and symptoms of ALL are gone

If a patient does not achieve remission after the first course of induction chemotherapy, that may indicate the first treatment approach is unlikely to work. In this situation, a "second-line" course of chemotherapy is given, usually using different drugs.

Even when a complete remission is achieved, some leukemia cells that cannot be seen with a microscope may still remain in the bone marrow. The presence of these cells is referred to as minimal/measurable residual disease (MRD). Patients who have achieved remission after initial treatment, but who still have MRD, are at increased risk of disease relapse. Testing for MRD can help doctors identify patients who may benefit from further treatment with intensified therapies such as allogeneic stem cell transplantation.

It is important to get tested for MRD after achieving remission. The tests used most commonly to detect MRD are flow cytometry, polymerase chain reaction (PCR) and next-generation sequencing. These tests typically use samples of bone marrow cells, but in some cases blood samples can be used. They are much more sensitive than standard tests that examine cell samples with a microscope.

It is often recommended that MRD testing be done after the completion of induction therapy. Recommendations for additional MRD testing depend on the treatment regimen that is used.

If you are in remission but test positive for MRD, your doctor may prescribe **blinatumomab (Blincyto®)**. Blinatumomab is approved by the US Food and Drug Administration (FDA) to treat adults and children with:

- B-cell ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1 percent
- Relapsed or refractory B-cell ALL

See the free LLS fact sheet *Minimal Residual Disease (MRD)* for more information.

Table 4. Some Drugs Approved or in Clinical Trials for the Treatment of ALL

Anthracyclines

- 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®)
- Calaspargase pegol-mknl (Asparlas™)
- 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

- Rituximab (Rituxan®)
- Blinatumomab (Blincyto®)
- Inotuzumab ozogamicin (Besponsa®)
- Tisagenlecleucel (Kymriah®)

Janus Kinase Inhibitor

- Ruxolitinib (Jakafi®)

New treatments 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). Postremission therapy refers to ALL treatments given to patients after their disease is in a complete remission. Even when patients test negative for MRD, some residual leukemia cells that cannot be detected even with very sensitive tests are believed to remain in the body after remission. So the optimal treatment for ALL patients requires additional intensive therapy after remission is achieved. As in the induction phase, individual factors such as the age of the patient, the ability to tolerate intensive treatment, cytogenetic test results, the availability of a matched stem cell donor and other considerations may influence the decision about the best treatment approach.

Consolidation Therapy. The second phase of treatment is called consolidation therapy. This phase can also include phases known as "intensification" therapy. Consolidation therapy begins once ALL is in remission. The goal of consolidation therapy is to kill any remaining leukemia cells that could cause a relapse.

Consolidation therapy typically consists of multi-agent intensive chemotherapy. For patients with Ph+ ALL, a TKI is usually continued. In addition, most treatment plans call for the continuation of CNS prophylaxis and treatment.

The specific combination of drugs and the duration of therapy for consolidation vary. Depending on the treatment regimen used, consolidation therapy may consist of entirely different drugs than those used during induction, or some of the same drugs that were successful in the induction phase, either at the same or higher doses. Consolidation therapy is usually given in cycles over 4 to 6 months.

Consolidation therapy protocols may include one or two intensified treatments that are similar to the ones used during the induction phase. These 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 phase may include:

- High-dose **methotrexate**
- **Cytarabine**
- **Vincristine**
- **6-mercaptopurine (6-MP)**
- **Cyclophosphamide**
- **Pegaspargase**
- Corticosteroids (**prednisone, dexamethasone**)

As part of consolidation therapy, some patients in remission may receive a stem cell transplant. Doctors usually recommend stem cell transplantation for patients whose ALL has high-risk genetic features or for patients who have high rates of MRD after initial therapy (called "persistent MRD).

Not everyone can have a stem cell transplant. It is an intense and complex treatment that can cause life-threatening side effects in some patients. Being able to have a transplant also depends on having a matched donor and an adult caregiver. See page 30 for more information on stem cell transplantation.

Maintenance Therapy. The third phase of treatment is called maintenance therapy. The goal of maintenance therapy is to prevent disease relapse after induction therapy and consolidation therapy.

Some drugs used in the maintenance phase are given orally and, typically, patients are treated in an outpatient setting. Patients 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.

Most maintenance therapy regimens include:

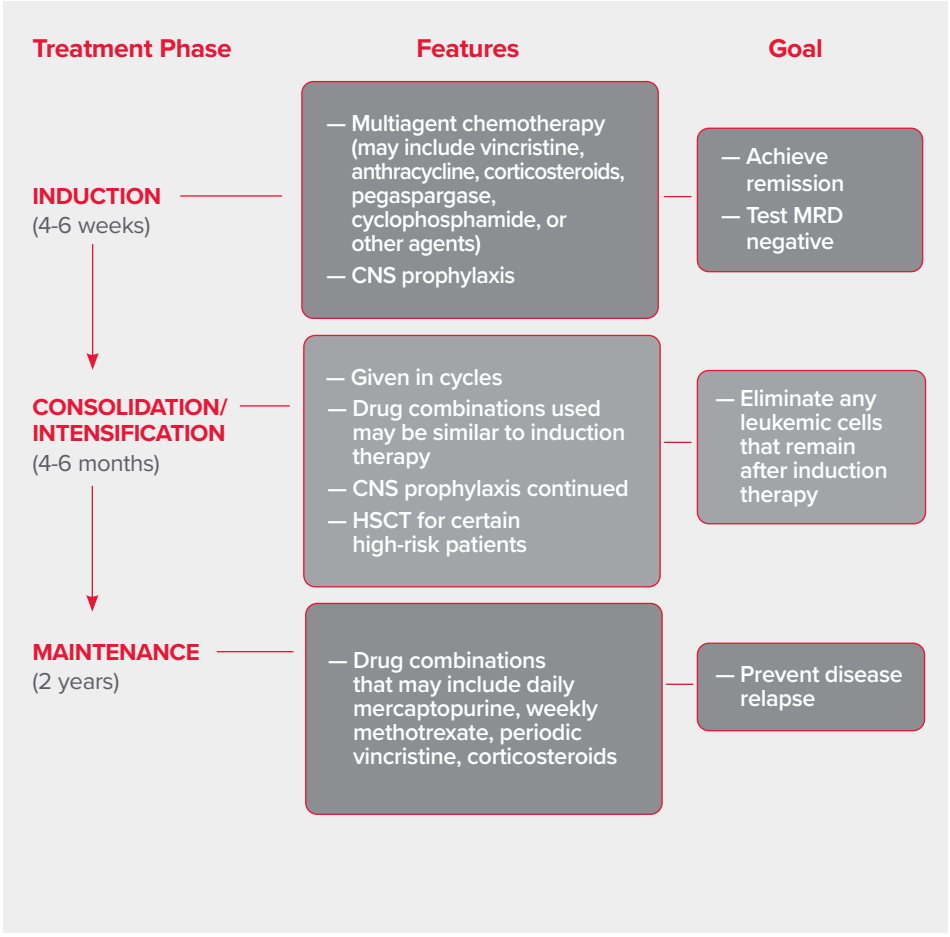
- **6-mercaptopurine** (administered daily)
- **Methotrexate** (administered weekly)
- Periodic doses of **vincristine** and corticosteroids

For patients with Ph+ ALL, a TKI is often included during the maintenance phase as well.

If you are taking an oral medication at home, it is important for you to take the medication as prescribed by the doctor. Not taking your mediation as prescribed by the doctor can increase the chance that the cancer will return (relapse).

For more information about oral drug adherence, please visit www.LLS.org/booklets to see the free LLS booklet *Oral Treatment Adherence Facts*.

Figure 4. Acute Lymphoblastic Leukemia (ALL) Treatment Overview



Abbreviations: CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease.

Types of Treatment. Not everyone with ALL receives the same type of treatment. Your doctor will tailor your treatment based on your ALL subtype and other factors such as your age, overall health and your response to treatment. In addition to chemotherapy, your treatment may include targeted therapy, immunotherapy and stem cell transplantation.

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 both cancer cells and normal, healthy cells. Different types of chemotherapy drugs work in different ways to kill leukemia cells or to stop new leukemia cells from forming. Therefore, more than one chemotherapy drug is frequently used.

Chemotherapy is usually given in treatment cycles. Each cycle is made up of a certain number of days of treatment, followed by a certain 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 are injected into a vein. During an intravenous (IV) infusion, the drugs are slowly injected into the vein over the course of a few hours, or several days in the case of a "continuous infusion." Often, IV chemotherapy is given through a thin, soft tube called a "central venous line," a "catheter," or a "central line." The central line is usually attached to a "port" or other device that is surgically placed under the skin, into the patient's upper chest, to allow access to the central line.

Targeted Therapy. Targeted therapy uses drugs or other substances that target and attack specific cancer cells, but are less likely to harm normal cells.

Tyrosine Kinase Inhibitors (TKIs). Tyrosine kinases are enzymes that are a part of many cell functions including cell signaling, growth and division. These enzymes may become too active in patients with an ALL subtype called Philadelphia chromosome-positive ALL (Ph+ ALL). The leukemia cells of these patients have the Philadelphia chromosome, which is formed by a translocation between parts of chromosome 9 and chromosome 22. This chromosomal alteration creates a fusion gene called *BCR-ABL1*, which overproduces tyrosine kinase and thereby causes leukemia cells to grow and divide uncontrollably.

TKIs work to block these overactive enzymes and may stop cancer cells from growing. TKIs are pills taken by mouth. They are generally not used alone to treat ALL. Instead, they are added to a combination chemotherapy regimen.

The following TKIs have been approved to treat Ph+ ALL:

- **Imatinib (Gleevec®),** taken by mouth, is used to treat:
  - Adult patients with relapsed or refractory Ph+ ALL
  - Pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy
- **Dasatinib (Sprycel®),** taken by mouth, is used to treat:
  - Adults with Ph+ ALL who no longer benefit from, or did not tolerate, other treatment
  - Children 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy.
- **Ponatinib (Iclusig®),** taken by mouth, used to treat adults who have:
  - Ph+ ALL who cannot receive any other tyrosine kinase inhibitor (TKI) medicines
  - *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 pain in muscles, bones and joints. 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.

In addition, another 10 to 30 percent of adults with ALL have a subtype known as Philadelphia chromosome-like ALL (Ph-like ALL). Unlike those with Ph+ ALL, who share a similar genetic mutation, patients with Ph-like ALL have a highly diverse range of genetic mutations that activate tyrosine kinase signaling. Researchers are working to understand better ways to identify these mutations and to determine whether specific TKIs can be effective.

Immunotherapy. Immunotherapy treatments use substances that can stimulate and/or suppress the immune system to help the body fight cancer. There are immunotherapy treatments that target proteins, called cluster of differentiation (CD) antigens, on the surface of leukemia cells. B-cell ALL is typically characterized by the presence of the proteins CD10, CD19, CD20, CD22, CD24 and CD79a. T-cell ALL is typically associated with the presence of CD3.

Monoclonal Antibodies. Monoclonal antibodies are proteins that are made in the laboratory. They can bind to substances in the body, including cancer cells. Most are designed to 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.

- **Blinatumomab (Blincyto®)** is a bispecific antibody used to treat adults and children with:
  - B-cell ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1 percent
  - Relapsed or refractory B-cell ALL

  Blinatumomab is a liquid that is administered slowly into a vein (by IV) as a continuous infusion over a period of 28 days. Hospitalization of the patient is typically recommended for the first few days of treatment. Side effects of blinatumomab may include:
  - Fever
  - Headache
  - Infection
  - Nausea
  - Diarrhea
  - Swelling
  - Neurological complications such as seizures, confusion, disorientation, slurred speech and loss of balance

- **Inotuzumab ozogamicin (Besponsa®)** is a monoclonal antibody linked to a chemotherapy drug that is indicated for the treatment of patients with relapsed or refractory B-cell ALL. Inotuzumab ozogamicin targets CD22, a surface protein 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 and then releases the chemotherapy drug, **calicheamicin**, causing the cell to die.

  Inotuzumab ozogamicin is administered by IV infusion and, for appropriate patients, can be given in an outpatient setting. Common side effects include increased risk of infections, bleeding, fatigue, fever, nausea, headache and abdominal pain. Liver injury is also seen and, in rare instances, can be serious and even fatal. Older patients, as well as patients with pre-existing liver disease and those who undergo stem cell transplantation, appear to be at greater risk of serious forms of liver toxicity.

- **Rituximab (Rituxan®)** is a monoclonal antibody that binds to CD20, a protein found on the surface of healthy B cells and on the lymphoblastic B cells of approximately 50 percent 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 instead 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-positive ALL. Side effects may include allergic reactions, infections, chills, fatigue, body aches and low blood cell counts.

Chimeric Antigen Receptor (CAR) T-Cell Therapy. Tisagenlecleucel (Kymriah®) is FDA-approved for the treatment of patients up to age 25 years who have B-cell ALL that is refractory or in second or later relapse. This treatment is designed to help the body's own immune system fight cancer.

Each dose is made for a specific patient, using the patient's own T cells (white blood cells that help the body fight infections and cancer). The T cells are collected from the patient and then genetically modified to add a new gene containing a CAR protein, so that the T cells can identify and kill leukemia cells with CD19 on their surfaces. These modified cells are infused back into the patient's bloodstream to kill the cancer cells.

While this treatment can be very effective, it is also associated with a relatively high rate of serious complications. As a result, it can only be given at specialized cancer centers that have expertise in delivering this form of treatment.

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

Stem Cell Transplantation. Some patients with ALL may benefit from stem cell transplantation. The goal of stem cell transplantation is to cure the patient's cancer by destroying cancer cells in the bone marrow with high doses of chemotherapy. Chemotherapy, however, can cause very serious side effects. Although administering higher doses of chemotherapy drugs can kill more leukemia cells, such high doses of chemotherapy can severely damage the stem cells in the bone marrow and may result in anemia, serious infections and uncontrolled bleeding. Stem cell transplantation allows doctors to give higher doses of chemotherapy than can typically be given. After the chemotherapy, the patient receives an infusion of healthy stem cells to replace those that were destroyed by the intensive chemotherapy. The healthy blood stem cells grow and multiply, forming new bone marrow and blood cells.

There are two main types of stem cell transplantation:

- Allogeneic—A patient receives stem cells from a matched or a partially matched donor, either related or unrelated to the patient.
- Autologous—A patient's own stem cells are collected before chemotherapy, stored and then given back to the patient after completing chemotherapy.

Stem cell transplantation is not used as the first or the primary treatment for ALL. It may be part of the treatment plan for high-risk ALL patients, or for patients who do not respond to other treatments.

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 your doctor. Your doctor will consider many factors, including your age, general health, certain

prognostic factors, previous treatments, and if you have a well-matched donor.

Allogeneic Stem Cell Transplantation. This is the most common type of stem cell transplantation used to treat ALL. In preparation for the transplant, patients are given high doses of chemotherapy, either with or without radiation therapy, to kill the remaining leukemia cells still present in the body. This part of the treatment, called "myeloablative conditioning," also kills cells in the bone marrow, including normal blood-forming cells. After the high-dose chemotherapy is completed, patients receive an infusion of the donor stem cells. 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 that helps the body fight infections and other diseases. The new immune system also has the potential to recognize and attack any remaining cancer cells in the body. The transplanted immune cells (called the "graft") identify the leukemia cells as foreign and destroy them. This is called the "graft-versus-leukemia (GVL) effect."

Allogeneic stem cell transplantation is associated with a higher rate of side effects and mortality than other treatment approaches. However, it may be considered a treatment option for patients with higher-risk ALL, based on cytogenetic and molecular test results. The decision to perform an allogeneic transplant also depends on the age of the patient and the patient's understanding of the potential benefits and risks.

Studies show that allogeneic stem cell transplantation may benefit adult ALL patients in the high-risk and intermediate-risk categories who are younger than 60 years and have a HLA-matched sibling donor. The timing of the 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.

One possible serious side effect of allogeneic transplantation is graft-versus-host disease (GVHD). This 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. GVHD can develop within weeks after transplantation or much later. A doctor can prescribe medications that can help prevent or minimize GVHD.

Reduced-Intensity Allogeneic Stem Cell Transplantation. This type of transplantation 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 transplant. The conditioning therapy in a reduced-intensity transplant uses lower doses of chemotherapy and/or radiation therapy. This therapy reduces the number of cancer cells, but it does not completely destroy the patient's bone marrow. As in standard allogeneic transplantation, the white blood cells from the donor may recognize any remaining leukemia cells as foreign and destroy them.

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

Autologous Stem Cell Transplantation. This is a procedure in which stem cells are removed from a cancer patient before the patient undergoes intensive chemotherapy, either with or without radiation therapy. The patient's removed stem cells are stored and then returned to the patient after the chemotherapy treatment.

Autologous transplantation is not commonly used to treat patients who have ALL, but it may be a treatment option for ALL patients participating in a clinical trial.

Talk to your doctor about

- Stem cell transplantation and ask whether it is a treatment option for you

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 Facts*.

Special Treatment Considerations

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL). About 25 percent of adults with ALL have a subtype called "Ph-positive ALL" (also known as "Ph+ ALL" or "Philadelphia chromosome-positive ALL"). The leukemia cells of these patients have the Philadelphia chromosome, which is formed by a translocation between parts of chromosomes 9 and 22. A piece of chromosome 9 attaches to chromosome 22, and a piece of chromosome 22 attaches to chromosome 9. The abnormal chromosome 22 is known as the Philadelphia chromosome. This chromosomal alteration creates a fusion gene called *BCR-ABL1*. This gene produces a protein called a tyrosine kinase that causes the leukemia cells to grow and divide out of control.

Patients who have Ph+ ALL are typically treated with tyrosine kinase inhibitors (TKIs), combined with chemotherapy. This combination has become the standard of care for Ph+ ALL patients. New combinations of drugs for the treatment of Ph+ ALL are also being studied in clinical trials. See *Tyrosine Kinase Inhibitors* on page 27 for more information on TKIs.

Philadelphia Chromosome-like (Ph-like) ALL. About 10 percent to 30 percent of adults have a subtype of B-cell ALL with genetic features similar to Ph+ ALL, but without the *BCR-ABL1* fusion gene that defines Ph+ ALL. Instead, patients have a highly diverse range of genetic mutations that activate tyrosine kinase signaling. Tyrosine kinases are enzymes that play a part in many cell functions, including cell signaling, growth and division. These enzymes may become too active in

leukemia cells. Tyrosine kinase inhibitors (TKIs) are drugs that work by blocking enzyme activity in a way that may prevent cancer cells from growing. Findings from recent studies that analyzed the genetic profile of patients with Ph-like ALL have suggested that using TKIs and other targeted therapies may help treat these types of leukemia.

Older Adolescents and Young Adults (AYA). The term "AYA population" generally refers to 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 center's protocol for this age group. Adult treatment regimens and pediatric treatment regimens differ 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. By 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 (CNS prophylaxis) is started earlier and given longer. Some children receive maintenance therapy for up to 3 years, while adults usually receive 2 years of maintenance therapy.

Researchers have found that AYA patients treated with pediatric protocols have improved rates of survival compared with patients of the same age who are treated with adult ALL protocols. Therefore, clinical trials are looking into the use of a variety of pediatric protocol options for AYA patients.

For more information on pediatric treatments, see the free LLS booklet *Acute Lymphoblastic Leukemia (ALL) in Children and Teens*.

Refractory and Relapsed ALL. Some patients have residual leukemia cells in their bone marrow even after they receive intensive treatment. In these cases, the disease is referred to as being "refractory" (or "refractory ALL"). Other patients achieve remission but later have decreased numbers of normal blood cells and a return of leukemia cells in their bone marrow. This is referred to as a "relapse" of the disease (or "relapsed ALL").

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

One option is to use different drugs than those used during the patient's induction regimen. These options, suggested by the NCCN guidelines, may include:

- **Blinatumomab (Blincyto®)** may be a treatment option for patients with ALL that has not responded to two or more TKIs.
- **Inotuzumab ozogamicin (Besponsa®)** is a treatment option for adults with either relapsed or refractory B-cell ALL.

- **Tisagenlecleucel (Kymriah®)** is a treatment option for patients up to 25 years old with relapsed or refractory B-cell ALL.
- Combination regimens that include several chemotherapy drugs, some of which may have been given in the past. Examples of such include
  - **Inotuzumab ozogamicin + mini-hyper CVD** (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine) for patients with B-cell ALL
  - **Augmented hyper-CVAD:** hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone and pegaspargase, alternating with high-dose methotrexate and cytarabine
  - **MOpAD:** methotrexate, vincristine, pegaspargase, and dexamethasone with rituximab for CD20-positive disease
- **Nelarabine,** alone or in combination with other drugs (e.g., nelarabine, etoposide, cyclophosphamide), for patients with T-cell ALL
- **Clofarabine,** alone or in combination with other drugs (e.g., clofarabine, cyclophosphamide, etoposide)
- **Vincristine sulfate liposome (Marqibo®)** injection for the treatment of adult patients with Ph-negative ALL in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies
- **Fludarabine-**based regimens
  - **FLAG-IDA:** fludarabine, cytarabine, granulocyte colony-stimulating factor ± idarubicin
  - **FLAM:** fludarabine, cytarabine and mitoxantrone
- **Cytarabine**-containing regimens (e.g., high-dose cytarabine, idarubicin, intrathecal methotrexate)
- Alkylator combination regimens (e.g., etoposide, ifosfamide, mitoxantrone)

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

New mutations in the *BCR-ABL1* gene may occur over time. Some mutations can lead to resistance to certain TKIs. Before a patient starts treatment, *BCR-ABL1* gene mutation testing should be done to look for new mutations that may cause certain TKIs to stop working. Each TKI works in a slightly different way. Certain TKIs may be able to counteract a mutation that other TKIs cannot. Results of the gene mutation test may explain why a TKI used for a person's initial treatment stopped working. A patient may then receive a different TKI. Many Ph+ ALL patients receive **imatinib (Gleevec®)** during induction therapy. In cases of disease relapse, **dasatinib (Sprycel®)** or **ponatinib (Iclusig®)** may be treatment options.

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

- **Blinatumomab (Blincyto®)**
- **Inotuzumab ozogamicin (Besponsa®)**
- **Tisagenlecleucel (Kymirah®)**

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

In refractory cases, different drugs than those used in the first course of treatment may be administered in an effort to induce remission. Stem cell transplantation is a potential option following remission, and it may result in a more durable remission. In relapsed cases, the duration of the remission, the patient's age and the results of cytogenetic tests may influence the decision about the best treatment approach.

Talk to your doctor about

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

Research and Clinical Trials

New treatment approaches for ALL are under study in clinical trials. 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. Every new drug or treatment regimen goes through a series of studies called "clinical trials" before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians, researchers and patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time you discuss your treatment with your doctor. Patient participation in past clinical trials has resulted in the Food and Drug Administration (FDA)-approved therapies we have today.

LLS Information Specialists, available 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. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, patients and

their caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit the LLS Clinical Trial Support Center at www.LLS.org/CTSC for more information.

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 this disease.

Genetics of Leukemia. Researchers are studying how changes (mutations) in the DNA of normal bone marrow cells can cause them to develop into leukemia cells. There is a need to identify these genetic variations in order to customize treatment options based on the genetic characteristics of the leukemia cells. Newer techniques in gene sequencing have revealed previously unknown mutations that may be involved in the development of ALL. This information will help researchers develop new targeted therapies, tailored to specific disease characteristics in each patient.

New Drugs and Treatment Regimens. Researchers are working to develop safer and more effective treatments for ALL. New treatments are needed for high-risk patients and for patients with relapsed and refractory disease. While ALL treatment can be very effective for most children, cure rates are lower for adults. Researchers are studying new drugs, as well as the use of existing drugs in different doses and with different methods of administration for adults with ALL. Treatment approaches under investigation include:

- Chemotherapy. Chemotherapy is still the main treatment for most cases of ALL. Researchers are now studying different combinations of chemotherapy drugs to determine which is most effective while also limiting side effects. And they are continuing to modify and reformulate traditional chemotherapy drugs to improve overall survival. They are also evaluating combinations of chemotherapy drugs with newer targeted therapies.
- Stem cell transplantation. Researchers continue to study stem cell transplantation to try to increase cure rates for ALL patients, reduce complications and determine which patients are most likely to benefit from this treatment.
- Targeted therapy. This is a type of treatment that uses drugs or other substances to block the action of certain enzymes, proteins or other molecules involved in the growth and survival of cancer cells, while causing less harm to healthy cells. Targeted agents under study include:
  - Proteasome inhibitors, such as **bortezomib (Velcade®)** and **carfilzomib (Kyprolis®)**
  - Janus Kinase (JAK) JAK1 and JAK2 inhibitors such as **ruxolitinib (Jakafi®)**
- Immunotherapy. **Tisagenlecleucel (Kymriah®)**—Chimeric antigen receptor (CAR) T-cell therapy is a type of immunotherapy that engineers a patient's own immune cells to recognize and attack cancer cells. Researchers are conducting research to see whether these treatments are effective in adults.

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. Mixed phenotype acute leukemia (MPAL), also known as "biphenotypic leukemia" or "mixed lineage leukemia," is a subtype of acute leukemia of ambiguous lineage. It is a combination of two forms of leukemia: acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). It accounts for 2 to 5 percent of all acute leukemias, affecting patients of all ages, and includes several different subtypes. The best approach to treatment has not been determined. There is no standard therapy for MPAL and, in general, it is associated with a poor prognosis. This is due to difficulty in correctly identifying this type of leukemia, its low incidence, the lack of experience in treating it, and its tendency to be resistant to both ALL and AML therapies. The reasons underlying this resistance are not yet clear, but it may be related to the high percentage of MPAL patients with high-risk chromosomal abnormalities.

Developing the best treatment approach involves a variety of factors. These include the patient's age, medical history (and other relevant medical conditions), and the characteristics of the leukemia cells as determined by immunophenotyping as well as genetic tests. It is also important to determine whether the patient has the Philadelphia chromosome-positive (Ph+) subtype, which accounts for about 25 percent of all cases of MPAL. Treatment for Ph+ MPAL usually consists of an ALL chemotherapy regimen, selected based on the patient's age, in combination with a tyrosine kinase inhibitor (TKI) and followed by allogeneic stem cell transplantation, if needed. For patients with a non-Ph+ MPAL subtype, the treatment typically consists of either an ALL regimen, or a combination of ALL and AML therapies, possibly followed by consolidation therapy with an allogeneic transplant, when a donor is available.

Side Effects and Complications

Side Effects of Chemotherapy. Most ALL treatment side effects are temporary and subside once the body adjusts to therapy, or after the therapy is completed. If side effects become severe, patients may need to be hospitalized.

Low Blood Cell Counts. Cancer and cancer treatments often cause drops in blood cell counts. This can result 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, a patient's 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, in order to reduce the chance for serious infections. The growth factors used most frequently are the granulocyte-colony stimulating factors, like **filgrastim (Neupogen®)** and **pegfilgrastim (Neulasta®)**.

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 in patients may be increased because chemotherapy damages the cells lining the mouth and intestines, making it easier for bacteria to enter the bloodstream. After a patient starts a course of chemotherapy, antibiotics are commonly given to prevent bacterial infection, as well as other drugs that prevent fungal and viral infections.

Because of the increased risk for infection, the medical staff and all family and friends need to practice frequent and vigorous handwashing and take other precautions to avoid exposing patients to bacteria, viruses and other infection-causing agents. The caregivers of patients who have central lines or ports need to be meticulous when cleaning insertion sites and catheters.

Patients at home should seek medical attention immediately if any signs of infection develop. A temperature of 100.4°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 with ALL are advised to receive certain vaccinations. For adult patients, these include vaccinations for influenza and pneumococcal pneumonia. Immunizations using live organisms or high viral loads, such as the herpes zoster/shingles vaccine **Zoster Vaccine Live (Zostavax®)**, should not be given to ALL patients. If a family member or friend receives a live vaccine, the patient should not go near the recently vaccinated person 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). This condition occurs when a large number of cancer cells die within a short period of time, releasing their contents into the blood. TLS can be severe at the time of initial leukemia diagnosis and during the early phases of treatment, especially for those who have very high white blood cell counts before induction therapy.

TLS 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, which changes 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 with leukemia are constantly monitored for the development of TLS and are given drugs, such as **allopurinol (Zyloprim®)** or **rasburicase (Elitek®)**, to prevent or lessen the effects of this condition.

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

- Hair loss
- Diarrhea
- Nausea and vomiting
- Mouth sores
- Rashes
- Headaches
- Loss of appetite
- Fatigue
- Neuropathy (pain, numbness, tingling or muscle weakness, usually in the hands or feet)

These short-term side effects usually go away once a patient has completed treatment. Fortunately, drugs that counteract nausea and vomiting can be given during treatment to 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. Corticosteroids are also frequently incorporated into consolidation and maintenance regimens. Side effects of corticosteroids may include high blood sugar (hyperglycemia) and corticosteroid-induced diabetes. Patients should be monitored to ensure that their glucose levels are under control. The development of stomach ulcers can be another side effect of corticosteroid therapy. Medicines that reduce stomach acid may be recommended during corticosteroid therapy to decrease the risk of gastric ulceration.

Drugs and other supportive therapies are available to prevent or manage many side effects. **For more information, visit www.LLS.org/booklets to view, print or order the free LLS series *Side Effects Management*.**

Sometimes drugs or drug combinations cause side effects that continue after treatment ends. Some effects may be long-lasting (see *Long-Term and Late Effects of Treatment* on page 41).

Follow-Up Care

After a patient completes treatment for ALL—including maintenance therapy—and is in remission, follow-up tests are done to check how well the treatment worked and to look for signs of relapse. The tests also check how well the patient's organs are working. This is important because 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 follow-up visits should continue indefinitely.

Table 5, below, lists examinations and tests that should occur during the first 3 years after treatment ends, based on National Comprehensive Cancer Network (NCCN) recommendations.

Table 5. NCCN Recommendations for Follow-Up Exams and Tests

Year	Tests	Frequency of Tests
Year 1	• Physical exam including testicular exam for males	Every 1 to 2 months
	• CBC with differential	Every 1 to 2 months
	• Liver function tests	Every 1 to 2 months until normal test results
	• Bone marrow aspirate and cerebrospinal fluid testing if there is a suspected relapse	As needed
	• For Ph+ ALL, testing of the *BCR-ABL1* gene for mutations	Periodically
Year 2	• Physical exam including testicular exam for males	Every 3 to 6 months
	• CBC with differential	Every 3 to 6 months
	• Bone marrow aspirate and cerebrospinal fluid testing if there is a suspected relapse • For Ph+ ALL, testing of the *BCR-ABL1* gene for mutations	As needed periodically
Year 3 and on	• Physical exam, including testicular exam for males	Every 6 to 12 months
	• CBC with differential • Bone marrow aspirate and cerebrospinal fluid testing if there is a suspected relapse • For Ph+ ALL, testing of the *BCR-ABL1* gene for mutations	Every 6 to 12 months As needed periodically

Adapted from National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia (Adult and AYA). 2020.

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

You may experience difficulties when you return to your daily routines after a long period of treatment. Getting support throughout this time, and for as long as needed, is important.

Long-Term and Late Effects of Treatment. While treatments for ALL have led to increased survival rates, some may cause significant long-term or late effects. Long-term effects of cancer treatment are medical problems that last for months or years after treatment ends. Late effects are medical problems that do not appear until years, or even possibly decades after treatment ends.

People who have been treated for ALL may be at increased risk for heart damage, other cancers and neurologic or cognitive problems. Patients should see 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. Various factors can influence the risk of developing long-term or late effects, including:

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

Most ALL patients are treated with an anthracycline, such as **daunorubicin** or **doxorubicin**. 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 treatment 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 than in younger children or adults (most likely due to skeletal growth). To monitor patients who are at risk of developing this condition, routine tests to measure calcium and vitamin D levels should be done and periodic evaluation with imaging tests should be considered.

Sometimes, cranial radiation is used for patients with obvious central nervous system (CNS) disease involvement, or those experience CNS relapse. To avoid the risk of long-term or late effects such as neurocognitive impairment or the development of a second cancer, doctors are limiting the use of this treatment, opting for drug-therapy alternatives as much as possible.

These and other possible long-term and late effects can be managed. For more information, see the free LLS booklet *Long-Term and Late Effects of Treatment in Adults Facts*.

Talk to your doctor about

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

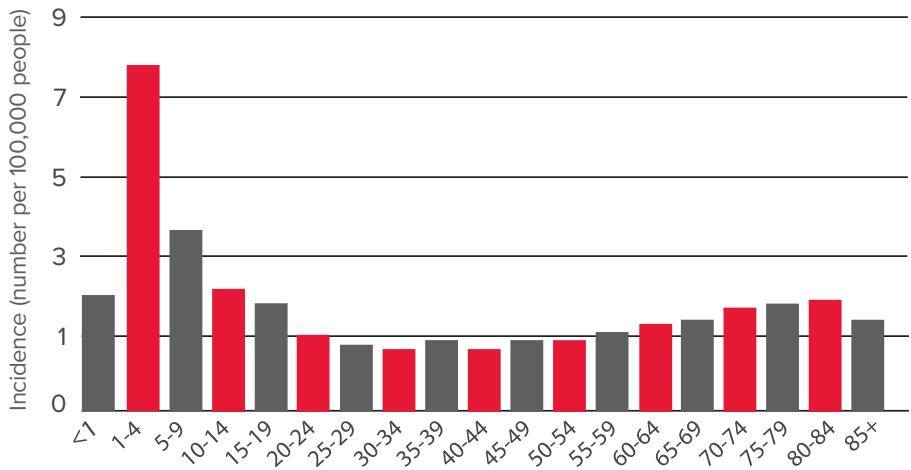
Treatment Outcomes. The cure rates and survival outcomes for patients with ALL have improved over the past few decades. Today, nearly 90 percent of adults diagnosed with ALL achieve a complete remission, which means that leukemia cells can no longer be seen in the bone marrow with a microscope. Still, despite high remission rates, relapses still commonly occur in adults and survival rates for adult patients remain at approximately 20 to 40 percent. However, these rates can vary significantly, depending on the patient's ALL subtype and other prognostic factors.

Incidence, Causes and Risk Factors

Incidence. Approximately 6,150 new cases of acute lymphoblastic leukemia (ALL) are expected to be diagnosed in the United States in 2020. In 2016, there were an estimated 70,308 people living with or in remission from ALL.

There is an unusual age distribution among patients with ALL. 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 are younger than 20 years at the time of diagnosis. See **Figure 5**, below.

Figure 5. Acute Lymphoblastic Leukemia (ALL): Age-Specific Incidence Rates 2012-2016



The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of ALL 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; 2019.

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 they cause ALL to develop. Not all patients with ALL have the same genetic mutations, and some genetic changes are more common than others. The DNA mutations associated with ALL are not usually inherited from a parent; more often they occur during a person's lifetime.

Although the cause is unknown, 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 for a disease may never develop it, while others with no known risk factors may develop the disease. ALL is not contagious.

Factors associated with an increased risk of developing ALL include:

- Exposure to chemotherapy and radiation therapy. People who have received 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. Because these are very uncommon disorders, it is highly unusual for a risk of ALL to be passed along or inherited in families.
- Age. Children and adolescents, and adults older than 70 years are at greater risk of developing ALL.
- Gender. Men are more likely than women to develop ALL.
- Race/ethnicity. In the United States, ALL is more common in Hispanics and whites.

Normal Blood and Bone Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients throughout the body. It also carries away waste products. 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:

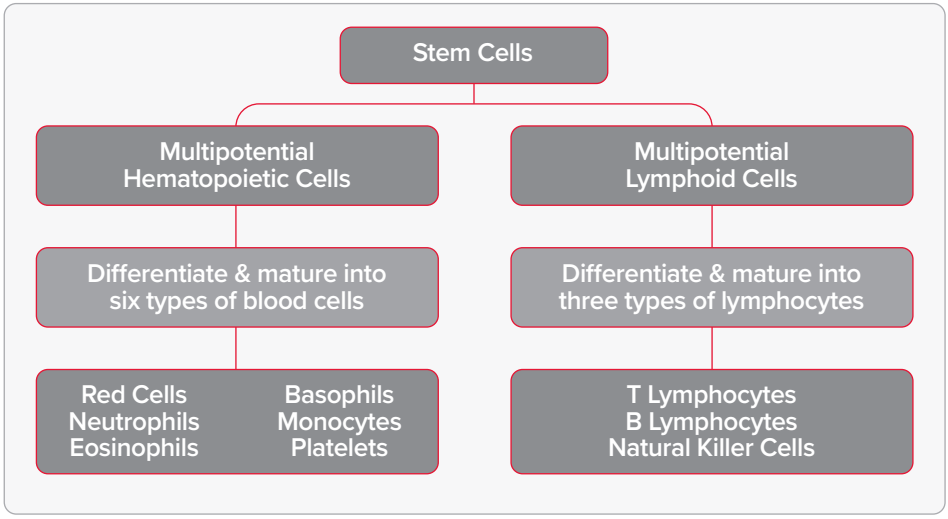
- Proteins
  - Albumin, the most common blood protein
  - Blood-clotting proteins (coagulation factors) made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
  - Immunoglobulins, proteins that help the body fight infection
- Hormones, such as thyroid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

Blood cells. Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called "hematopoiesis." The blood cells are suspended in the plasma. See **Figure 6** on page 46.

Once the stem cell is created, it will develop into one of the three types of blood cells:

1. Red blood cells (the cells that carry oxygen)
    - These make up a little less than half of the body's total blood volume.
    - They are filled with hemoglobin, the protein that picks up oxygen from the lungs and takes it around the body. It binds with carbon dioxide (CO_2) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO_2 is removed from the lungs.
2. Platelets (cells that help blood clot)
    - These are small cells (one-tenth the size of red blood cells).
    - They help stop bleeding from an injury or cut.
    - They stick to the torn surface of the vessel, clump together and plug up the bleeding site. They form a clot with the help of proteins such as fibrin, and electrolytes such as calcium.
3. White blood cells (or WBCs, the cells that fight infections), including:
    - Neutrophils and monocytes. These are cells called "phagocytes" that ingest and destroy bacteria and fungi. Unlike red blood cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
    - Eosinophils and basophils. These are the WBCs that respond to allergens or parasites.
    - Lymphocytes. These are the WBCs found mostly in the lymph nodes, spleen and lymphatic channels that are a key part of the immune system. Some enter the bloodstream. There are three major types of lymphocytes:
        - T lymphocytes (T cells)
        - B lymphocytes (B cells)
        - Natural killer cells (NK cells)

Figure 6. Blood Cell & Lymphocyte Development



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

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

In babies, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have blood-forming marrow. In adults, marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull. Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be used for transplants. Some stem cells enter the bloodstream and circulate. Doctors know how to stimulate the growth of these cells in the marrow and make them migrate into the bloodstream. Then a special technique called “apheresis” is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

Resources and Information

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

For Help and Information

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

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

Clinical Trials Support Center (CTSC). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Please visit www.LLS.org/CTSC for more information.

Free Information Booklets. LLS offers free education and support booklets that can be either 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. Please visit www.LLS.org/programs for more information.

Financial Assistance. LLS offers financial assistance to individuals with blood cancer. Please 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

LLS Health Manager™ App. This free mobile app helps you manage your health by tracking side effects, medication, food and hydration, questions for your doctor, and more. Export the information you've tracked in a calendar format and share it with your doctor. You can also set up reminders to take medications, hydrate, and eat. Please visit www.LLS.org/HealthManager to download for free.

One-on One Nutrition Consultations. Access free one-on-one nutrition consultations with a registered dietitian who has experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management, and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition to schedule a consultation or for more information.

Podcast. The *Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other health care professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Please visit www.LLS.org/TheBloodline for more information and to subscribe.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens. Please visit www.LLS.org/SuggestedReading to find out more.

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

Community Resources and Networking

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Please visit www.LLS.org/community to join.

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

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), local 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 to obtain our directory.

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). Please visit www.LLS.org/espanol for more information.

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

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information please

- Call: the VA (800) 749-8387 (select option 4)
- Visit: www.publichealth.va.gov/exposures/AgentOrange

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

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

For more information, please

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

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

Health Terms

Alkylating Agent. A type of chemotherapy drug used in cancer treatment. It kills cancer cells by damaging their DNA, which prevents them 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 receiving high doses of chemotherapy and/or radiation therapy. **See the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

Anemia. A 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.

Anthracycline. A type of chemotherapy that is used to treat 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 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 substance that creates an immune response in the body, especially the production of antibodies. Examples include allergens, chemicals, bacteria, viruses and other substances outside the body. Cells in the body, including cancer cells, also have antigens on their surfaces that can cause an immune response.

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

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

Biopsy. A procedure to remove a sample of 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: 1) red blood cells that carry oxygen; 2) white blood cells that fight infections; and 3) platelets that help stop bleeding.

Bone Marrow. A spongy tissue in the hollow central cavity of the bones, where blood cells form.

Bone Marrow Aspiration. A procedure in which a liquid sample of bone marrow is removed for examination by a pathologist. After the patient is given a numbing agent, a sample is taken (usually from the patient's hip bone) using a special needle. Bone marrow aspiration and bone marrow biopsy are often done at the same time, and may be done in the doctor's office or in a hospital.

Bone Marrow Biopsy. A procedure in which a sample of bone with bone marrow is removed for examination by a pathologist. A sample is usually taken from the hip 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 are often done at the same time, and may be done in the doctor's office or in a hospital.

CBC. See Complete Blood 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 given to lower the risk of leukemia cells spreading to the central nervous system (brain and spinal cord). The treatment may include intrathecal chemotherapy (chemotherapy directly injected into the cerebrospinal fluid, the space between the layers of tissue that cover the brain and spinal cord), high-dose chemotherapy injected into a vein, or radiation therapy.

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. Treatment that uses a patient's own T cells (a type of white blood cell) to identify and attack cancer cells. The T cells are taken from the patient's blood and sent to a laboratory, where they are genetically modified to attack cancer cells. The engineered T cells are then multiplied and later re-infused into the patient's blood stream. **See the free LLS fact sheet, *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts*.**

Chromosome. Part of a cell that contains genes in a linear order. Human cells have 23 pairs of chromosomes. **See the free LLS booklet, *Understanding Genetics*.**

Clinical Trial. A carefully planned and monitored research study to evaluate 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 increase survival time. A treatment that is proven to be 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).

Computed Tomography (CT) Scan. A procedure in which a series of x-ray images is processed with 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. This treatment consists of high-dose chemotherapy and/or total body radiation.

Cord Blood Stem Cells. Stem cells collected from the placenta and umbilical cord after a baby is born. These stem cells can be infused into a patient's bloodstream to replace damaged or disease stem cells in patients who undergo stem cell transplantation.

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 doctors diagnose specific types of blood cancer, determine appropriate treatment approaches and monitor treatment response in patients.

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

DNA. Abbreviation for deoxyribonucleic acid, the molecules found inside cells that carry genetic information. DNA 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 cell function and, in some cases, cancer.

Echocardiogram. A computer-generated 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 type of white blood cell that is released during infections and allergic reactions.

Erythrocyte. See Red Blood Cell.

FDA. The abbreviation commonly used to refer to 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 presence of tumor markers on the cell's surface. During this test, cells flow through an instrument called a "flow cytometer." When the cells pass through its laser beam, those with antibody-specific features light up and can be counted.

Fluorescence In Situ Hybridization (FISH). A technique for studying abnormal chromosomes in cells and tissues. Pieces of DNA 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 specialized microscope. This test can help diagnose some cancers, plan treatment and monitor the effectiveness of treatment.

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

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

Granulocyte. A type of white blood cell that has many particles (granules). Neutrophils, eosinophils and basophils are types of granulocytes.

Growth Factor. A substance made by the body that stimulates the growth of specific cells. Some growth factors are made in the laboratory and used as treatment. For example granuloctye-colony stimulating factor (G-CSF) is a substance made in the laboratory to increase the number of neutrophils after chemotherapy.

Hematologist. A doctor who specializes in treating blood diseases.

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

Hematopoiesis. The formation of new blood cells. For more information on the blood cell development process, see *Normal Blood and Bone Marrow* on page 44.

Hematopoietic Stem Cell. An immature cell that can develop into any type of blood cell including: a red blood cell, a white blood cell or a platelet.

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."

Human Leukocyte Antigen (HLA). A type of protein found on cells that helps the body distinguish its own cells from foreign cells. HLA factors are inherited from a person's mother and father. HLAs make up a person's tissue type, which varies from person to person, and are a critically important factor in allogeneic (donor) stem cell transplantation. 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 (markers) on the surface of the cells.

Immunotherapy. The term for several different treatment approaches used by doctors to harness the body's immune system in order to treat leukemia and other diseases. These include monoclonal antibody therapy, CAR T-cell therapy, radioimmunotherapy and vaccine therapy.

Intrathecal. The fluid-filled space between the thin layers of tissue that cover the brain and the spinal cord. In some situations (for example, when leukemia cells are in the central nervous system), 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 inserted 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-shaped 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: 1) B lymphocytes, which produce antibodies to help combat infections; 2) T lymphocytes (T cells), which have several functions, including assisting B lymphocytes (B cells) in making antibodies; and 3) natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Lymphoid. Referring to a lymphocyte (a type of white blood cell).

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.

Minimal Residual Disease (MRD). The small amount of cancer cells that may remain in the body after treatment, even when blood and bone marrow may appear to be normal. These residual cancer cells can only be identified by very sensitive tests. Also called "measurable residual disease." **See the free LLS fact sheet, *Minimal Residual Disease*.**

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 to target cancer cells.

Monoclonal Antibody Therapy. Targeted treatment using proteins made in the laboratory that either react with or attach to antigens on the cancer cells.

Monocyte/Macrophage. A type of white blood cell that forms in the bone marrow. Some monocytes travel through the blood to tissues in the body, where they become macrophages. Macrophages can combat infection in the tissues, ingest dead cells and assist lymphocytes in immune functions.

Mutation. A change in the DNA sequence of a cell. A mutation may be caused by an error in cell division, or by contact with DNA-damaging substances in the environment.

Neutropenia. A condition in which the number of neutrophils, a type of white blood cell, is below normal. People with low neutrophil counts are susceptible to infections

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

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

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

Petechiae. Pinhead-sized red or purple 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 phagocytes. Once an infection occurs, phagocytes migrate from the bloodstream and enter the infected tissue.

Philadelphia Chromosome (Ph Chromosome). An abnormality of chromosome 22 that occurs 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 between chromosomes 9 and 22 results in the creation of a fusion gene, called *BCR-ABL1*, on chromosome 22.

Plasma. The liquid portion of the blood, in which the blood cells, platelets, proteins and various other components are suspended. Also referred to as “blood plasma.”

Platelet. A small, colorless blood cell fragment that helps control bleeding. Platelets travel to and then collect at the site of a wound. The platelets’ sticky surface helps them form clots at the site of the wound and stop bleeding. Also called “thrombocyte.”

Polymerase Chain Reaction (PCR). A very sensitive genetic 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. PCR testing essentially increases (amplifies) small amounts of specific pieces of DNA so that they are easier to detect and measure. This test can find a single cancer cell among more than 500,000 to 1,000,000 healthy blood cells.

Port. A small device that facilitates access to a central line. It is used to withdraw blood 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, which is a thin flexible tube that is inserted into a large vein.

Prognosis. The probable outcome or expected course of a disease; the likelihood of recovery or recurrence of disease.

Protocol. A plan for medical treatment.

Radiation Therapy. The use of x-rays and other forms of radiation to treat cancer and other diseases.

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

Red Blood Cell. A type of blood cell that contains a protein called hemoglobin. Hemoglobin carries oxygen from the lungs to the tissues of the body. Red blood cells make up about 40 to 45 percent of blood volume in healthy people. Also called "erythrocyte."

Reduced-Intensity Stem Cell Transplantation. A type of allogeneic stem cell transplantation in which patients receive lower doses of chemotherapy drugs and/or radiation as preparation for the transplant. The chemotherapy and radiation do not completely kill all 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 a traditional high-dose or myeloablative allogeneic stem cell transplant—especially for older patients. **See the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.**

Refractory Cancer. Cancer that does not go into remission or improve substantially after 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, usually following treatment.

Resistance (Resistant) to Treatment. When cancer cells continue to grow, even after administration of intensive 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. Also called "drug resistance."

Risk Factor. A scientifically-established factor 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 (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. The spleen filters blood, stores blood cells and destroys old blood cells. Enlargement of the spleen is called "splenomegaly."

Stem Cell. A cell from which other types of cells develop. In the bone marrow, blood-forming stem cells mature into red blood cells, white blood cells and platelets. Stem cells can be collected, preserved and used for stem cell therapy. See Hematopoiesis.

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

Thrombocytopenia. A condition in which the number of platelets in the blood is below normal.

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

Transfusion. A procedure in which whole blood or parts of blood are placed into a patient's bloodstream.

Translocation. A genetic abnormality in which a piece of one chromosome breaks off and attaches to another chromosome. The location at which the break occurs may affect nearby genes and lead to medical problems. See Mutation. **See the free LLS booklet *Understanding Genetics*.**

Treatment cycle. A course of treatment followed by a period of rest to allow the body to recover. For example, chemotherapy given daily for 1 week followed by 3 weeks of rest might be one cycle of treatment.

Tyrosine Kinase Inhibitor (TKI). A type of drug that blocks the action of enzymes called "tyrosine kinases." Tyrosine kinases play a key role in cell function, affecting both cell growth and division. These enzymes may be too active, or found at very high levels, in some types of cancers. TKIs work to block these over-active enzymes and may stop cancer cells from growing.

White Blood Cell. A blood cell that is part of the body's immune system. The five major types of white blood cells are: neutrophils, eosinophils, basophils, monocytes and lymphocytes. Also called "leukocyte."

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

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