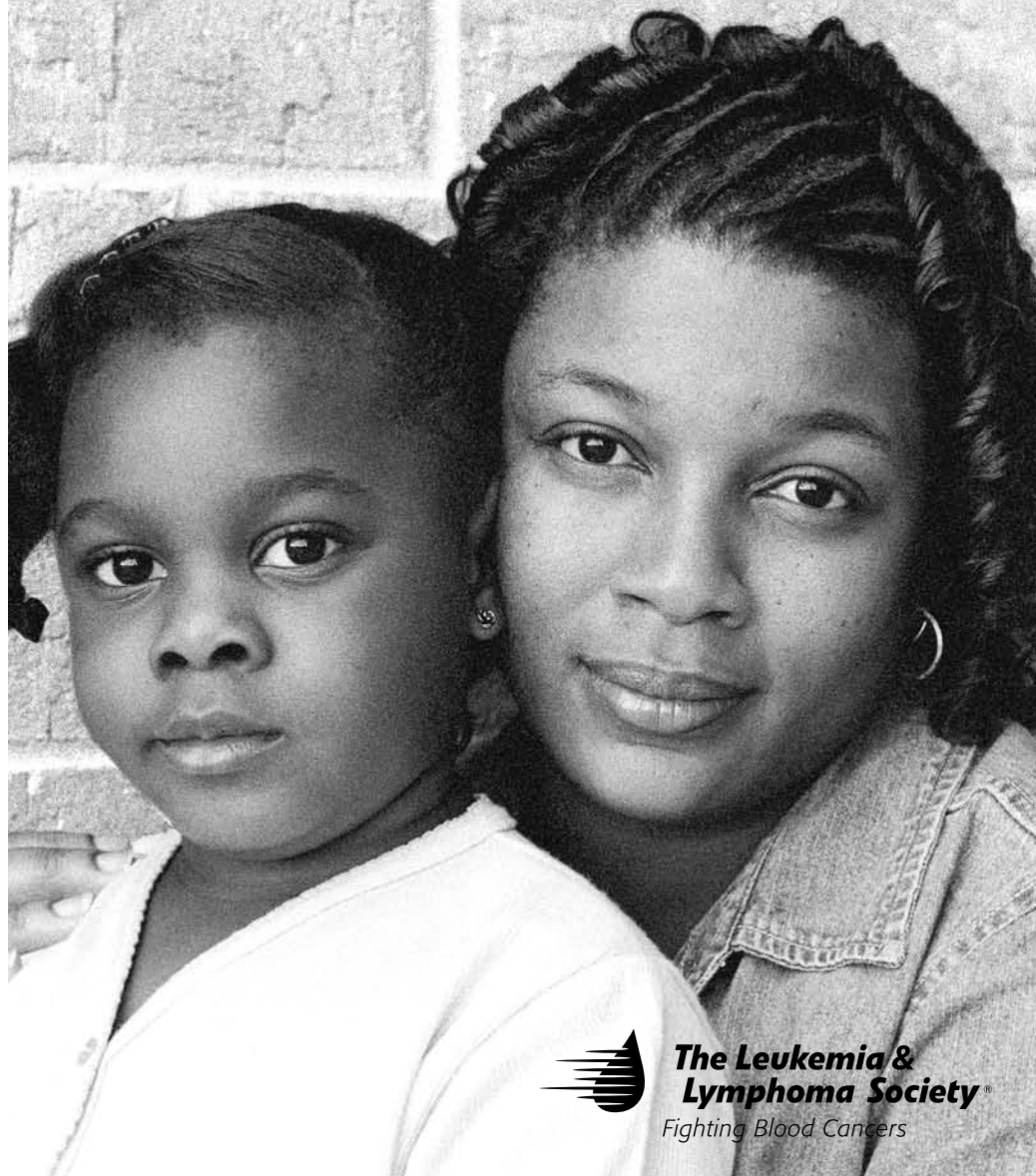


Acute Lymphocytic Leukemia

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Introduction

This booklet provides information about acute lymphocytic leukemia for patients and their families. A glossary is included at the end of the booklet to help readers understand medical terms that may be new. We hope this information is of assistance, and we welcome comments about the information in the booklet.

About 3,930 new cases of acute lymphocytic leukemia are diagnosed each year in the United States (Surveillance, Epidemiology and End Results [SEER] Program, 2006). It is the most common type of leukemia in children under the age of 15. About 60 percent of new cases of this disease are diagnosed in children, but it can occur at any age. Acute lymphocytic leukemia may be called by several names, including acute lymphoid leukemia and acute lymphoblastic leukemia.

Brief descriptions of normal blood and marrow and the lymphatic system are provided for background, followed by a detailed description of acute lymphocytic leukemia and its treatment.

This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is distributed as a public service by The Leukemia & Lymphoma Society, with the understanding that The Leukemia & Lymphoma Society is not engaged in rendering medical or other professional services.

Normal Blood and Marrow

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

- Proteins (such as albumin)
- Hormones (such as thyroid hormone)
- Minerals (such as iron)
- Vitamins (such as folate)
- Antibodies, including those we develop from our vaccinations (such as poliovirus antibodies).

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

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

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

Blood passes through the marrow and picks up formed red and white cells, and platelets, for circulation.

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

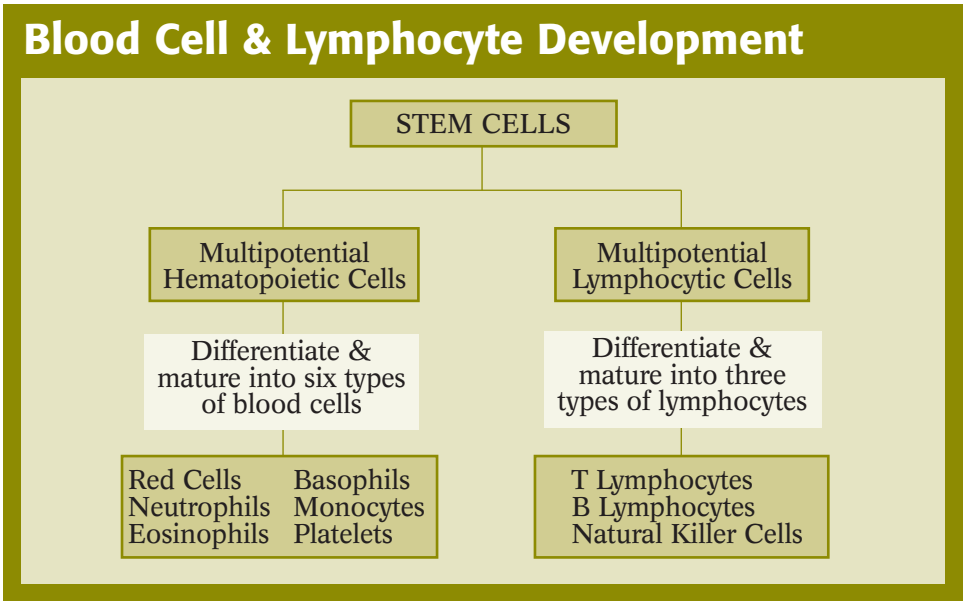


Figure 1. This simplified diagram shows the process of hematopoiesis. This process involves the development of functional blood and lymphatic cells from stem cells.

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

Some stem cells enter the blood and circulate. They are present in such small numbers that they cannot be counted or identified in the usual type of blood counts. Their presence in the blood is important because they can be collected by a special technique. If enough stem cells are harvested from a compatible donor, they can be transplanted into a recipient.

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

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

The Lymphatic System

The lymphatic system and the blood cell-forming system in the marrow are closely related. Most lymphocytes are found in the lymph nodes and other parts of the lymphatic system such as the skin, spleen, tonsils and adenoids (special lymph nodes), intestinal lining and, in young people, the thymus (see Figure 2). The lymphocytes circulate through channels called lymphatics that connect the lymph nodes scattered throughout the body. The lymphatic channels collect into large ducts that empty into a blood vessel. The lymphocytes enter the blood via these ducts. There are three types of lymphocytes. T lymphocytes (T cells) originate in the thymus, hence the designation “T.” The B lymphocytes (B cells) originate in the marrow in bone, although the “B” comes from the word “bursa,” an organ in birds that was first found to be the source of B lymphocytes. B lymphocytes make antibodies in response to foreign antigens, especially microbes. Collections of B lymphocytes are present in the marrow, which is an important site for their function.

The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibodies attach to the microbe and, in so doing, make it possible for other white cells to ingest and kill it. The white cells recognize the antibody and pull (ingest) it into the cell with its attached microbe. The cell can then kill and digest the microbe.

The third type of lymphocyte, natural killer (NK) cells, attacks virus-infected cells as a natural function without requiring antibody or other mediation. T cells and NK cells have other functions as well and are important elements in studies that are designing immunotherapies to treat leukemia and other cancers.

Leukemia

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

The major forms of leukemia are divided into four categories. The terms “myelogenous” or “lymphocytic” denote the cell type involved. Myelogenous and lymphocytic leukemia each have an acute or chronic form. Thus, the four major types of leukemia are acute or chronic myelogenous and acute or chronic lymphocytic leukemia. The term “acute lymphocytic leukemia” is synonymous with “acute lymphoblastic leukemia.” The latter term is used more frequently to denote this disease in children.

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

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

Acute Lymphocytic Leukemia

Acute lymphocytic leukemia (ALL) results from an acquired genetic injury to the DNA of a single cell in the marrow. The disease is often referred to as acute lymphoblastic leukemia because the leukemic cell that replaces the normal marrow is the (leukemic) lymphoblast. The effects are: 1) the uncontrolled and exaggerated growth and accumulation of cells called “lymphoblasts” or “leukemic blasts,” which fail to function as normal blood cells and 2) the blockage of the production of normal marrow cells, leading to a deficiency of red cells (anemia), platelets (thrombocytopenia) and normal white cells (especially neutrophils, i.e., neutropenia) in the blood.

ALL occurs most often in the first decade of life but increases in frequency again in older individuals (see Figure 3).

Acute Lymphocytic Leukemia Age-specific Incidence Rates 2000-2003

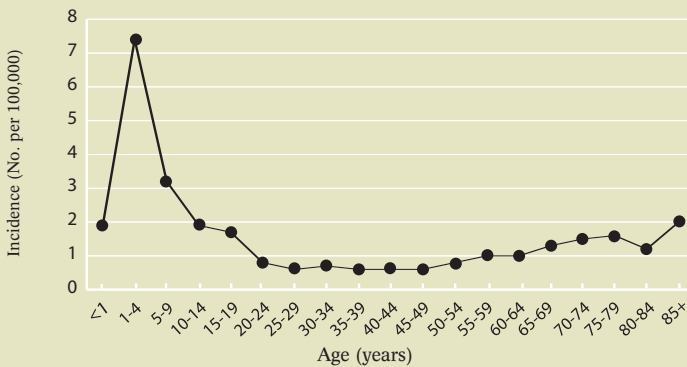


Figure 3. The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of ALL per 100,000 in a given age-group. Note that the risk of ALL is greatest in the first 5 years of life. An increase in occurrence is also seen in older individuals. (Data from the National Cancer Institute Surveillance, Epidemiology and End Results [SEER] Program, 2006.)

Causes and Risk Factors

The cause of acute lymphocytic leukemia is not clear. Few factors have been associated with an increased risk of developing the disease. Exposure to high doses of radiation, as carefully studied in the survivors of atomic bomb detonations in Japan, is one such factor. ALL occurs at different rates in various locations. There are higher leukemia rates in more developed countries and in higher socioeconomic groups. These and other findings have led to a hypothesis that reducing children's exposure to bacterial infections during the first year of life may have increased the risk of childhood ALL. However, there have been other life-saving benefits from avoidance of bacterial infections during infancy.

Scientists continue to explore possible relationships with lifestyle or environmental factors. Given the amount of study, this suggests that a number of complex factors may be involved. It is extremely disconcerting to patients and their families to wonder what they may have done differently to avoid the disease. Unfortunately, at the present time there is no answer to that question.

Some cases of ALL relate to a mutation in a lymphocyte that occurs during the prenatal period (in utero). Usually the leukemia is diagnosed in infancy or the first few years after birth. However, in some cases, years may elapse before the disease appears. Since there are more mutations found in utero than there are cases of childhood ALL, it appears that additional genetic abnormalities occurring after birth are needed to trigger the disease.

Subtypes of Acute Lymphocytic Leukemia

Acute lymphocytic leukemia can develop from primitive lymphocytes that are in various stages of development (see Table 1). The principal subtypes or phenotypes are uncovered by a test on the leukemic lymphoblasts called “immunophenotyping.” (“Phenotype” is the term used to describe the physical characteristics of a cell.)

The principal phenotypes are T-lymphocyte and B-lymphocyte types, so named because the leukemia cell has physical traits that are similar to normal T or B lymphocytes. About 88 percent of cases arise at some stage of B-lymphocyte development and the remainder of cases arises during some stage of T-lymphocyte development. Most cases of B-cell type ALL originate in a cell early in B-lymphocyte development and are referred to as “precursor B-cell type.”

Once these cell types are determined, the terms used to categorize the patient’s leukemia include acute T-lymphoblastic leukemia, acute B-lymphoblastic leukemia and acute precursor, or B-cell, lymphoblastic leukemia.

Other markers on the lymphoblasts that can be detected with immunophenotyping and may be useful to the physician include CD10, the common acute lymphoblastic leukemia antigen, abbreviated cALLa.

Examination of leukemic cells by cytogenetic techniques permits identification of chromosomes or gene abnormalities in the cells. For example, about 25 percent of children have an excess of chromosomes in their leukemic cells. This is referred to as hyperdiploidy, a term for more than the normal number of 46 chromosomes. This finding is associated with a favorable prognosis, whereas fewer than the normal number of chromosomes, referred to as hypoploidy, suggests a poor prognosis. Many other chromosome abnormalities may be associated with ALL. Another common alteration is a translocation between chromosomes 12 and 21. (A translocation occurs when a piece of one chromosome breaks off and sticks to the end of another chromosome.)

Table 1. Subtypes of Acute Lymphocytic Leukemia

Immunophenotypes

B-lymphocytic lineage subtypes These cases are identified by finding cell surface markers on the leukemic blast cells that are identical to those that develop on normal B lymphocytes. Almost 90 percent of cases are of the precursor B or B-cell subtype.

T-lymphocytic and Natural Killer (NK) cell lineage subtypes These cases are identified by finding cell surface markers on the leukemic blast cells that are identical to those that develop in normal T lymphocytes. About 10 percent of cases are of the T- and NK-cell subtypes.

Chromosome Abnormalities

Injury to chromosomes can be assessed by cytogenetics. The specific alteration in chromosomes aids in subclassifying acute lymphocytic leukemia. For example, a change in chromosome number 22, referred to as the Philadelphia or Ph chromosome, which occurs in a small percentage of children and a larger percentage of adults with acute lymphocytic leukemia, places the patient in a higher risk category. The approach to therapy would be intensified in those subsets of patients.

The immunophenotype and chromosome abnormalities in the leukemic cells are very important guides in determining the intensity of the drug combinations to be used in treatment and the duration of treatment.

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

Symptoms and Signs

Most patients feel a loss of well-being. They tire more easily and may feel short of breath during physical activity. They may have a pale complexion from anemia. There may be signs of a very low platelet count. These include black and blue marks that occur for no apparent reason or because of a minor injury, the appearance of pinhead-sized red spots under the skin called petechiae or prolonged bleeding from minor cuts. Discomfort in the bones and joints may occur. Fever in the absence of an obvious cause is common. Leukemic lymphoblasts may accumulate in the lymphatic system and lymph nodes can be enlarged. The leukemic cells can collect on the lining of the brain and spinal cord and lead to headache or vomiting.

Diagnosis

Blood and marrow cells are examined to diagnose the disease. In addition to low red cell and platelet counts, examination of the stained (dyed) blood cells with a light microscope will usually show the presence of leukemic blast cells. This is confirmed by examination of the marrow with bone marrow aspiration and biopsy, which almost always shows leukemic cells (see Figure 4). The blood and/or marrow cells are also used for studies of the number and shape of chromosomes (cytogenetic examination), immunophenotyping and other special studies, if required.

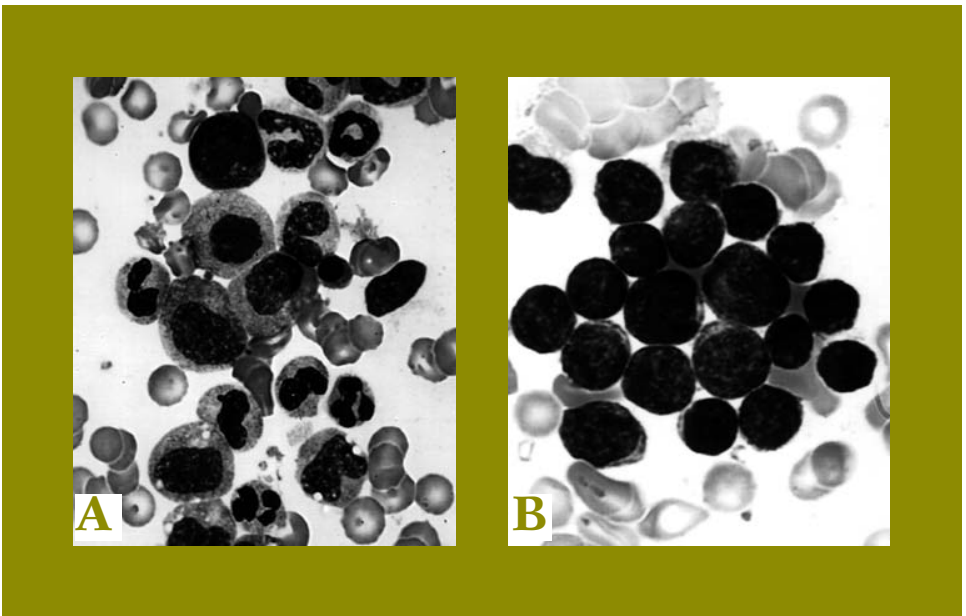


Figure 4. Panel A shows a photograph of developing cells in healthy marrow that have been placed on a glass slide and stained with dyes to make the cells more distinctive. The variation in the appearance of the cells is characteristic of normal marrow. Panel B shows a photograph of marrow cells from a patient with acute lymphocytic leukemia. An unvaried appearance of leukemic blast cells is present.

Treatment

The treatments for acute lymphocytic leukemia are described in this section.

Chemotherapy

Patients with ALL need chemotherapy as soon as possible after diagnosis. The principal goal of treatment is to bring about a remission with no evidence of leukemic blast cells in the blood or marrow, restore normal blood cell production and return blood cell counts to normal levels.

It is important to seek treatment in a center where physicians are experienced in the care of patients with acute leukemia. For most patients, intensive chemotherapy is required to achieve complete remission. Several drugs are combined to treat patients initially. Table 2 on page 13 lists the drug groups and individual drugs that may be used to treat this disease. Treatment approaches are undergoing intensive study throughout the world, and there are variations on the general descriptions given here. Thus, a patient may receive either a different number of drugs, sequence of drugs, or types of drugs than described here and be receiving appropriate and effective treatment. The age of the patient, the presence of few or many leukemia cells in the blood and the type of leukemic lymphocytes as judged by their appearance, immunophenotype or chromosome composition can influence the type of treatment given.

An indwelling catheter (central line) is placed in a vein in the upper chest in order to prepare a patient for treatment – to allow easier access for infusion of drugs or blood cells and for the removal of blood samples for cell counts and chemical tests.

Some patients build up uric acid in the body from their disease or from treatment. Uric acid, a breakdown product of cells, enters the blood and is excreted in the urine. If many cells are killed simultaneously by therapy, the amount of uric acid in the urine can be so high that uric acid kidney stones could form, which might interfere with the flow of urine. Patients with a high level of uric acid may be given a drug called allopurinol to minimize the buildup of uric acid in the blood. Allopurinol is given by mouth. Another drug, rasburicase, given as a single intravenous dose, can rapidly lower an elevated uric acid level.

Table 2. Some Drugs Used in the Treatment of Acute Lymphocytic Leukemia

Most antileukemic drugs interact with DNA, the genetic material in the cell. Each type of drug works in a different way to kill the cells. Combining drug types can strengthen the effects of the drugs. New drug combinations are being studied.

Antitumor Antibiotics

These drugs interact directly with the DNA in the nucleus of cells, interfering with cell survival.

- daunorubicin (daunomycin,
- rubidomycin, Cerubidine®)
- doxorubicin (Adriamycin®, Rubex®, Doxil®)
- mitoxantrone (Novantrone®)
- idarubicin (Idamycin®)

DNA-repair Enzyme Inhibitors

These drugs act on certain proteins (enzymes) that help to repair injury to DNA. These drugs prevent the enzymes from working and make the DNA more susceptible to injury.

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

DNA Synthesis Inhibitors

This drug reacts with DNA to alter it chemically and prevent cell growth.

- carboplatin (Paraplatin®)

DNA Damaging Agents

Agents that are related to mustard gas have been developed to interact with and disrupt and damage DNA.

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

Enzymes That Prevent Cells From Surviving

- asparaginase (Elspar®)
- pegaspargase (PEG-L asparaginase, Oncaspar®)

Tyrosine Kinase Inhibitors

- imatinib mesylate (Gleevec®)
- dasatinib (Sprycel™)

Antimetabolites

These are chemicals that are very similar to natural building blocks of DNA or RNA. They are changed from the natural chemical sufficiently so that when they substitute for it, they block the cell's ability to form RNA or DNA, preventing the cell from growing.

- 5-azacytidine (Mylosar®)
- clofarabine (Clolar®)
- cytarabine (cytosine arabinoside, Ara-C, Cytosar®, DepoCyt®)
- cladribine (Leustatin®)
- fludarabine (Fludara®)
- hydroxyurea (Hydrea®, Droxia®)
- mercaptopurine (Purinethol®)
- methotrexate
- thioguanine (Tabloid®)
- nelarabine (Arranon®)

Drugs That Prevent Cells From Dividing

These drugs interfere with structures in the cell that are needed to permit cells to divide. This effect can limit the growth rate of leukemia cells.

- vincristine (Oncovin®, Vincasar®)

Synthetic Hormones

A class of hormones that, when administered in large doses, can kill leukemia cells.

- prednisone
- prednisolone
- dexamethasone

Induction Therapy

Induction therapy is the term used for the initial phase of drug treatment. The specific drugs used, the doses used, and the timing of their administration depend on several factors, including the patient's age, the features of the leukemia and the general health of the patient. Several drugs are combined. Table 3 gives examples of the drugs used today for induction and post induction treatment.

Table 3. Examples of Therapies Used in the Treatment of Acute Lymphocytic Leukemia

Induction therapy given in first month

- Doxorubicin by vein
- Asparaginase by injection into muscle
- Vincristine by vein
- Dexamethasone by mouth
- Methotrexate by injection into the spinal fluid
- Cytarabine by injection into the spinal fluid

Post induction therapy given in cycles for two years

- Vincristine by vein
- Prednisone or dexamethasone by mouth
- Mercaptopurine by mouth
- Methotrexate by mouth, vein, or into muscle
- Methotrexate in the spinal canal
- Cytarabine by injection into the spinal fluid
- Hydrocortisone by injection into the spinal fluid
- Radiation therapy to the head

Central Nervous System Prophylaxis

Acute lymphocytic leukemia cells often collect in the lining of the spinal cord and brain, called the meninges. If not treated, the meninges can harbor leukemia cells, and relapse can occur in this site (meningeal leukemia). For this reason, treatment called central nervous system prophylaxis is also directed to those sites. The treatment involves injecting drugs, such as methotrexate, into the spinal column, or irradiating the covering of the central nervous system using x-rays. Sometimes both forms of treatment are used. These areas of the body that are less accessible to chemotherapy when given by mouth or in the vein are sometimes referred to as “sanctuary sites.”

Ph-positive ALL

About one out of four to five adults with ALL and a small number of children (about two to four percent) with ALL have a type called Ph-positive (or Philadelphia-positive) ALL. Patients with this subtype of ALL have a chromosome alteration that results in a specific gene mutation, referred to as BCR-ABL. These patients are treated with the drugs imatinib mesylate (Gleevec®) or dasatinib (Sprycel™) in addition to other multidrug chemotherapy. Imatinib and dasatinib each specifically block the leukemia-causing effects of the BCR-ABL gene mutation in many patients. Either one of these drugs given alone would not result in cures for ALL patients, so imatinib or dasatinib is combined with other drugs. Studies are ongoing to learn the usefulness of this approach for Ph-positive ALL. Another new drug, nilotinib (Tasigna™), is being studied in clinical trials for the treatment of Ph-positive ALL.

Childhood Versus Adult Forms of ALL

Acute lymphocytic leukemia has an unusual pattern of age distribution (see Figure 3, page 7). In the other types of leukemia, older people are more likely to develop the disease. In ALL, young children are most likely to develop the disease. The risk of developing the disease peaks at age 4 and then decreases until about age 50. At age 50, the incidence increases again, especially among men.

Although remission rates and duration have improved in adults, current therapy has not resulted in the high rate of extended remissions (greater than 5 years) and cures that are possible for children. The adult form of ALL is more resistant to treatment than is the childhood form of ALL; new and better adult ALL treatments are needed.

Post Remission Therapy

Since residual leukemia cells that are undetectable by blood or marrow examination remain after remission, the optimal treatment of ALL requires additional intensive post remission therapy. As in the induction phase, individual factors such as age of the patient, the ability to tolerate intensive treatment, cytogenetic findings, the availability of a stem cell donor and other considerations may influence the approach used. In most cases, post remission chemotherapy also includes drugs not used during induction treatment (see Table 3).

Minimal Residual Disease

Sensitive molecular techniques permit the identification of small amounts of residual leukemia cells at times when blood and marrow appear normal. This approach can be used if the leukemia cell has a detectable molecular abnormality. It can also permit more sensitive follow-up of patients in remission and can help determine whether additional treatment is necessary.

Stem Cell Transplantation

Patients between the ages of approximately 1 and 50 years who are in remission and have an HLA-matched donor are candidates for allogeneic stem cell transplantation. This is a technique that can restore the marrow of patients after intensive chemotherapy or radiation therapy. The transplant requires the marrow of a healthy donor who had the same tissue type (HLA type) as the patient. The source may be an “HLA-matched” brother or sister or unrelated donor with a matching tissue type. These stem cells can be frozen and stored in a manner similar to that of a blood bank, making them available to potential recipients who do not have related (sibling) donors with similar tissue types.

The decision to perform a transplant depends on the features of the leukemia, the age of the patient, and the patient’s (or his or her family’s) understanding of the potential benefits and risks.

Autologous stem cell infusion, another therapy for some types of leukemia, involves harvesting the patient’s own stem cells from blood or marrow, freezing them for later use, then thawing and infusing them into the patient after intensive chemotherapy or radiation therapy. Certain ALL patients may be considered for an autologous stem cell infusion if they are not eligible for allogeneic stem cell transplantation and they have not responded well to other treatments.

A child with a good prognosis would not be a candidate for stem cell transplantation unless his or her course was marked by a poor response to treatment or a relapse. The high rate of cure for children with ALL who are treated with chemotherapy decreases the frequency with which stem cell transplantation is considered. For children who do undergo transplantation, the use of unrelated, tissue type (HLA)-matched donors appears to be just as successful as it is for related, matched donors (e.g., siblings), making more donors available through stem cell registries.

Treatment Side Effects and Their Management

Acute lymphocytic leukemia decreases the production of normal blood cells, and the levels are further decreased by the effects of chemotherapy. When chemotherapy is effective, developing blood cells as well as leukemic cells are eliminated from the marrow, resulting in a severe deficiency of red cells (anemia), phagocytes (neutropenia and monocytopenia) and platelets (thrombocytopenia) in the blood. Transfusion of red cells and, often, platelets may be required, and it is likely that therapy to prevent or treat infection due to a low white cell count will be necessary. Red cell and platelet transfusions are usually effective in providing sufficient amounts of those cells until the beneficial effects of treatment occur and blood cell counts return toward normal.

A rise in temperature or the onset of chills may be the only signs of infection in a patient with a very low white cell concentration. In these patients, persistent coughing, tenderness at a site prone to infection, sore throat, pain on urination or frequent loose stools may also be signs of an infection. Efforts to decrease the risk of infection with vigorous hand washing by all visitors and medical staff, and meticulous care of central line sites, are important. Central lines may result in infection or in thrombosis (clot formation). These effects require antibiotics or anticoagulant therapy and may often require removal of the central line. Care of the gums, a site of bacterial growth, is another important area of infection prevention.

Antibiotic therapy is used to treat infection caused by the deficiency of phagocytes (monocytes and neutrophils, microbe-eating cells). The bacteria and fungi normally present on skin and in the nose, mouth or large bowel (colon), or transferred from other persons or the environment, are likely to establish infection during this period. Methods of harvesting white cells from normal donors have improved, so that blood phagocytes can be obtained in quantities sufficient to transfuse children and smaller adults, if the severity of the infection and an inadequate response to antibiotics warrant such treatment.

The use of blood cell growth factors, which stimulate the production of phagocytes, can shorten the period during which the white cell count is low. The growth factors used most frequently are granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). These agents are only used in children in special circumstances.

In most patients normal blood cell production will return after several weeks and transfusion of cells and antibiotics will no longer be needed. Blood cell counts gradually approach normal, well-being returns and leukemia cells cannot be identified in blood or marrow. This is a remission. In this state, residual leukemia cells are inactive. They do not interfere with normal blood cell development but have the potential to regrow and cause a relapse of the leukemia. For this reason, additional treatment in the form of chemotherapy usually continues.

Chemotherapy affects tissues that require a high rate of cell birth (cell division) to keep them functioning. High rates of cell turnover occur in the lining of the mouth, the lining of the intestines, the skin and the hair follicles. This explains why mouth ulcers, diarrhea, and hair loss are common after chemotherapy. Rashes may also occur.

Nausea and vomiting can be a distressing feature of treatment. The causes can be complex. The effects are the result of actions on the intestines and on centers in the brain that, when triggered, lead to vomiting. Fortunately, drugs that counteract the nausea and vomiting can be given to prevent or relieve these distressing side effects if they occur. Some ALL patients find that acupuncture treatments relieve chemotherapy-associated nausea and vomiting.

Refractory Leukemia and Relapsed Leukemia

Since most children are cured of their disease, the problem of refractory and relapsed leukemia has become less frequent. However, some children and many adults have residual leukemia cells in their marrow even after intensive treatment. This circumstance is referred to as “refractory leukemia.” Some patients who have had a remission of leukemia after therapy have a return of leukemia cells in the marrow and a decrease in normal blood cells. This situation is referred to as a “relapse.”

In the case of refractory leukemia, the approaches used in an effort to induce remission may include drugs not used in the first course of treatment or stem cell transplantation.

In people who relapse, the duration of the remission, the patient's age and the cytogenetic findings in the leukemia cells influence the approach to therapy. Drugs similar to those initially used to treat the leukemia, different drugs or stem cell transplantation may be used.

Clofarabine is used to treat relapsed and refractory ALL. It is indicated for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory ALL after they have received at least two prior regimens.

In studies all over the world, scientists are working to develop approaches to increase the number of patients who have a remission and to increase the duration of remission and the frequency of cures.

Follow-up

Patients who are in remission should continue to be examined regularly by their physicians. After the induction of remission and the completion of post remission therapy, careful periodic assessment of the patient's state of health, blood cell counts and, if necessary, marrow is important. As time progresses, the interval between assessments may be lengthened, but assessments should be continued indefinitely. Although current therapy for ALL can be curative for most children, there may be long-term effects of therapy, including effects on growth, cognitive development and psychosocial development. Because of these possible effects, long-term follow-up and appropriate ongoing counseling are important. Follow-up studies on childhood leukemia treatment are ongoing. For more information, see the Society's free fact sheet, *Long-Term and Late Effects of Treatment for Blood Cancers*.

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

Clinical Trials

New approaches to therapy are under study in clinical trials. These trials, conducted under rigorous guidelines, help physicians to determine the beneficial effects of new treatments and what, if any, adverse effects they have. New drugs, new types of immunotherapy and new approaches to stem cell transplantation are continually being explored to bring new and better treatments to the patient. The Society's Information Resource Center offers guidance on how patients can work with their physicians to find out if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct clinical trial searches for patients, family members and healthcare professionals. Information Specialists can be called at (800) 955-4572. The service is also available on the Society's Web site, www.LLS.org. The number of patients with ALL who enter remission, stay in remission for years or are cured has increased significantly over the past 30 years (see Figure 5). Several areas of research have contributed to this progress.

In children, the probability of an extended remission or cure has increased from less than 3 percent in 1964 to a 5-year survival rate (in children under 15 years old) of 87 percent (SEER, 2006) as a result of successful treatments made possible by clinical trials.

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

Leukemia-specific Therapy

Increasingly, clinical studies are identifying leukemia by more specific criteria than the appearance of the leukemia cells. These additional factors include the type of chromosome abnormality, the presence of multidrug resistance characteristics, the immunophenotype, and others. New and different drug regimens are being tested in situations that are likely to be refractory to the usual chemotherapy. These and other new approaches, many of which are being supported by the research programs of The Leukemia & Lymphoma Society, hold the promise of increasing the rate of remission and finding cures for all blood cancers.

Five-Year Relative Survival Rates for Acute Lymphocytic Leukemia in Children Under 15 Years, 1964-2002

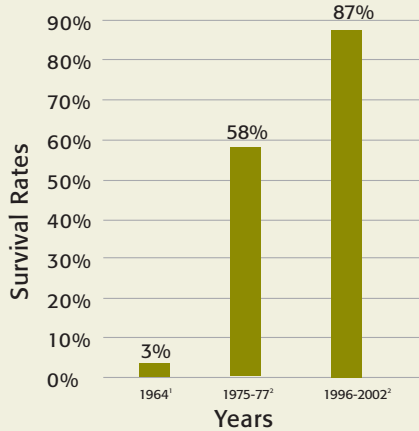


Figure 5. Horizontal axis shows years. Vertical axis shows five-year relative survival rates (percentage) for children under 15 years of age. The graph shows that childhood ALL 5-year relative survival rates have improved significantly over the past four decades.

Sources: 1. Zuelzer WW. Implications of long-term survivals in acute stem cell leukemia of childhood treated with composite cyclic therapy. *Blood*. 1964;24:477-494. 2. Surveillance, Epidemiology and End Results (SEER) Program. Cancer Statistics Review, 1975-2003. National Cancer Institute; 2006.

New Drug Treatments

Extensive testing is being conducted to synthesize new drugs or find them from natural (botanical) sources. These drugs are first tested for their usefulness in the laboratory and then, through the method of clinical trials, on patients. Researchers are also investigating new combinations of existing drugs for their usefulness in the treatment of leukemia and other blood cancers.

Drug Resistance

The leukemia cells of some patients are not as easily killed by drugs as those of other patients. This may lead to a failure of current treatment. Research has uncovered mechanisms in the leukemia cell that protect it from the effects of chemotherapy. As these mechanisms are defined, ways of reversing drug resistance are also being developed. In general, there are two mechanisms for drug resistance:

- 1) Specific genes encode proteins that probably evolved to protect the stem cells from toxins. Examples of these proteins are P-glycoprotein (multidrug resistant protein), lung resistance protein, and breast cancer resistance protein, named for the tissue from which they were identified. However, they each may play a role in mechanisms of acute leukemia cells by decreasing the effectiveness of chemotherapy.
- 2) Gene families normally control programmed cell death, which is the pathway of action of chemotherapy. Chemotherapy accentuates and accelerates programmed death of cancer cells. In some blood cancers, these genes are down-regulated or blocked; thus, cancer cell death as a result of chemotherapy is blocked.

No successful clinical approaches have been found as yet, even though trials of experimental drugs that block one or another of these pathways have been studied. This probably reflects the multiple ways in which cancer cells may avoid drug action, and blocking one method may not be sufficient. In cell cultures, antisense oligonucleotides can block the production of proteins that produce multidrug resistance. It is hoped that clinical trials of such agents may occur soon. Research in this area continues.

Immunotherapy

Research is being conducted on several approaches that may enhance the body's natural defenses. The goal is to kill or prevent the growth of leukemia cells. Radioimmunotherapy is an example of immunotherapy. This approach combines antibodies with attached isotopes that emit irradiation. These antibodies can be made in the laboratory. They are injected into the patient to destroy leukemia cells. Another approach uses normal lymphocytes that can attack leukemia cells because they have been immunized to recognize the leukemia cells as foreign or abnormal.

Cytokines

These naturally occurring chemicals can be made commercially using the techniques of biotechnology. These chemicals can be used to help restore normal blood cells during treatment or enhance the immune system to attack the leukemia.

Oncogenes

Defining the precise changes (mutations) in DNA that cause a normal cell to be transformed into a leukemia cell is leading to the development of new therapies. One example of this is the treatment of Ph-positive ALL with imatinib or dasatinib, which target the BCR-ABL oncogene (cancer-causing gene). New therapies could block the effects of other oncogenes and the cancer-causing proteins that the genes direct the cells to make.

Imatinib treatment with chemotherapy is effective for many Ph-positive ALL patients. Dasatinib, another drug targeting the BCR-ABL oncogene, is now available for patients who do not tolerate or respond to imatinib or who develop resistance to it. Another drug targeting the BCR-ABL oncogene, nilotinib, is being studied in clinical trials as a useful alternative for patients with intolerance or resistance to imatinib or dasatinib. Both dasatinib and nilotinib are more potent than imatinib and can be effective for a proportion of Ph-positive ALL patients.

Gene Expression Profiling

Current research suggests that the use of molecular techniques, including gene expression profiling, may supplement or replace epidemiologic risk factors. These studies may also help identify molecular targets for leukemia-specific therapy. The development of laboratory methods that assess the overexpression or underexpression of genes in leukemic cells compared to normal cells can give reliable patterns of gene expression that may correlate with the outcome of treatment. The changes in gene expression may also provide targets for new therapies.

Social and Emotional Aspects

The diagnosis of leukemia may provoke a profound emotional response in the patient, family members and friends. Denial, depression, a feeling of hopelessness, and fear are just a few of the emotions many persons diagnosed with leukemia experience. No one response is either expected or unexpected.

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

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

Children’s Concerns

Children with cancer may feel frightened and helpless but may be too young to fully understand their illness or the treatment and its implications. Children with blood cancers may be dealing with absence from school, separation from friends and an inability to participate in certain activities, such as sports – at least for a time. Children who are ill may feel anger toward their healthcare team for “hurting” them, or toward their parents for allowing them to become ill or for having to undergo treatment. Reengaging the child in as many activities as possible is one of the best ways to soothe and reassure the child and minimize disruptions in the child’s development. Siblings of the child with cancer may also require special attention. They may fear that the disease will strike them, feel guilt about their brother’s or sister’s illness and receive less time from parents who devote extra time to their ill child.

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

Treatment Choices

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

Family and Friends

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

Lifestyle Changes

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

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

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

Glossary

Absolute Neutrophil Count

The number of neutrophils, a type of white cell, a person has to fight infection. “ANC” is another term for absolute neutrophil count.

Allogeneic Stem Cell Transplantation (see Stem Cell Transplantation)

Anemia

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

Antibodies

Proteins released by plasma cells that recognize and bind to specific foreign substances called antigens. Plasma cells are derived from B-lymphocytes. Antibodies coat, mark for destruction or inactivate foreign particles like bacteria, viruses or certain chemicals such as harmful toxins. Antibodies can also be made in the laboratory. These can be polyclonal antibodies (derived from different B-lymphocyte lines) or monoclonal antibodies (derived from a single B-lymphocyte line). Monoclonal antibodies produced in the laboratory can be used to target and destroy specific types of cancer cells.

Apheresis

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

Autologous Stem Cell Infusion

This technique, often referred to as transplantation, involves 1) harvesting the patient's stem cells from blood or marrow, 2) freezing them for later use and 3) thawing and infusing them via an indwelling catheter after the patient has been given intensive chemotherapy or radiation therapy. The blood or marrow may be obtained from a patient with a disease of the marrow (for example, acute myelogenous leukemia) when in remission or when the marrow and blood are not overtly abnormal (for example, in lymphoma). Technically, this procedure is not transplantation, which implies taking tissue from one individual (the donor) and giving it to another person (the recipient). The purpose of this procedure is to restore blood cell production from the preserved and reinfused stem cells after intensive therapy has severely damaged the patient's remaining marrow. This procedure can be performed using marrow or blood stem cells. The latter can be harvested by hemapheresis. (See the Society's free booklet *Blood and Marrow Stem Cell Transplantation*.)

Banding of Chromosomes

The staining of chromosomes with dyes that highlight transverse bands or regions on the chromosome. The bands give the chromosomes more specific features, allowing individual distinctions to be made among them. This technique permits more precise identification of chromosomes.

Basophil

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

Blast Cells

This term refers to the earliest marrow cells identified by the light microscope. Blasts represent about 1 percent of normally developing marrow cells. They are largely myeloblasts, which are cells that will develop into neutrophils. In normal lymph nodes, blasts are lymphoblasts; that is, cells that are part of lymphocyte development. In the acute leukemias, blast cells, similar in appearance to normal blast cells, accumulate in large numbers, constituting perhaps up to 80 percent of all marrow cells. In acute myelogenous leukemia, myeloblasts accumulate, and in acute lymphocytic leukemia, lymphoblasts accumulate. Sometimes the distinction between myeloblasts and lymphoblasts can be made by examination of stained marrow cells through the microscope. Often, immunophenotyping or use of special staining of marrow cells is required to be sure of the distinction.

Bone Marrow

The bones are hollow and their central cavity is occupied by marrow, a spongy tissue that is the site of blood cell formation. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. In the adult, the bones of the hands, feet, legs and arms do not contain marrow in which blood cells are made. In these sites the marrow is filled with fat cells. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried throughout the body.

Bone Marrow Aspiration

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

Bone Marrow Biopsy

A test to examine marrow cells to detect cell abnormalities. This test differs from a marrow aspiration (defined above) in that a small amount of bone filled with marrow is removed, usually from the hip bone. After medication is given to numb the area, a special biopsy needle is used to remove a core of bone containing marrow. The marrow is examined under a microscope to determine if abnormal cells are present.

Bone marrow aspiration and biopsy may be done in the doctor's office or in a hospital. The two tests are almost always done together. Both tests are also done after treatment to determine the proportion of blood cancer cells that have been killed by therapy.

Bone Marrow Transplantation (see Stem Cell Transplantation)

Central Nervous System (CNS) Prophylaxis

In certain types of leukemia, particularly acute lymphoblastic leukemia and acute monocytic leukemia with high blood cell counts, there is a propensity of the leukemic cells to enter the covering of the spinal cord and brain (the meninges). This process is often not apparent until months or years after remission when the leukemia returns, first in the coverings of the central nervous system, then in the marrow and blood. To prevent this type of relapse (meningeal leukemia), virtually all children and adults with acute lymphocytic leukemia who enter remission are treated by placing appropriate chemotherapy in the space that bathes the spinal cord and brain to prevent the leukemia from returning in these sites. In some cases, x-ray therapy is administered to the head as well. These approaches are very effective in eliminating leukemia cells in the coverings of the brain and spinal cord.

Chemotherapy

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

Chromosome

The nucleus of all human cells contains 46 structures called chromosomes. The genes, specific stretches of DNA, are the principal structures that make up the chromosomes. An “average-sized” chromosome contains enough DNA to account for about 2,000 genes. This gives rise to the estimate that the human genome has about 90,000 genes (46 x 2,000). The genes on the X and Y chromosomes, the sex chromosomes, are the determinants of our gender: two X chromosomes in females and an X and a Y chromosome in males. The number or shape of chromosomes may be altered in lymphoma or leukemia cells.

Clonal (Monoclonal)

A population of cells derived from a single transformed (neoplastic) parent cell. Virtually all cancers are derived from a single cell with an injury or mutation to its DNA and thus are monoclonal. The mutated cell has an alteration in its DNA that causes it to form an oncogene and leads to its transformation into a cancer-causing cell. The clone (cancer) is the total accumulation of cells that grow from the single mutated cell. Leukemia, lymphoma and myeloma are examples of clonal cancers; that is, cancers derived from a single abnormal cell.

Colony-Stimulating Factor (CSF) (see Cytokines)

Computed Tomography (CT) Scan

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

Cord Blood Stem Cells

Stem cells that are present in blood drained from the placenta and umbilical cord. These stem cells have the capability to repopulate the marrow of a compatible recipient and produce blood cells. Frozen cord blood is a source of donor stem cells for transplantation to HLA-matched recipients. Most cord blood transplants are given by matched or nearly matched unrelated donors.

Cycle of Treatment

The term designates an intensive, clustered period of chemotherapy (and/or radiotherapy). The treatment may be given for several days or weeks and represents one cycle of treatment. The treatment plan may call for two, three or more cycles of treatment.

Cytogenetics

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

Cytokines

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

Differentiation

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

Eosinophil

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

Erythrocytes (see Red Cells)

A synonym for red cells.

Granulocyte

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

Granulocyte Colony–Stimulating Factor (G-CSF) (see Cytokines)

Granulocyte-Macrophage Colony–Stimulating Factor (GM-CSF) (see Cytokines)

Growth Factors (see Cytokines)

Hematologist

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

Hematopathologists are pathologists who specialize in the diagnosis of blood cell diseases and who perform the specialized laboratory tests often required to make a conclusive diagnosis.

Hematopoiesis

This term describes the process of blood cell development in the marrow. The most undeveloped cells in the marrow are stem cells. They start the process of blood cell development. The stem cells begin to develop into young or immature blood cells like red cells or white cells of various types. This process is called “differentiation.” The young or immature blood cells then further develop into fully functional blood cells. This process is called “maturation.” The cells then leave the marrow and enter the blood and circulate throughout the body. Hematopoiesis is a continuous process that is active normally throughout life. The reason for this activity is that most blood cells live for short periods and must be continuously replaced. Red cells die in four months, platelets in 10 days and most neutrophils in two or three days. About 500 billion blood cells are made each day. This requirement for very rapid replacement explains the severe deficiency in blood cell counts when the marrow is injured by replacement with leukemia cells.

HLA

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

Immunophenotyping

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

Indwelling Catheter

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

Karyotype

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

Leukocytes (see White Cells)

A synonym for white cells.

Leukopenia

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

Lymphatic System

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

Lymph Nodes

Small structures, the size of beans, that contain large numbers of lymphocytes and are connected with each other by small channels called lymphatics. These nodes are distributed throughout the body. In patients with lymphoma and some types of lymphocytic leukemia the malignant lymphocytes grow and expand the lymph nodes so that they may become enlarged. This enlargement of lymph nodes can be seen, felt, or measured by a CT scan or MRI, depending on the degree of enlargement and location.

Lymphocyte

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

Lymphokines (see Cytokines)

Magnetic Resonance Imaging (MRI)

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

Marrow (see Bone Marrow)

Monocyte (Macrophage)

A type of white cell that represents about 5 to 10 percent of the cells in normal human blood. The monocyte and the neutrophil are the two major microbe-eating and killing cells in the blood. When monocytes leave the blood and enter the tissue, they are converted to macrophages. The macrophage is the monocyte in action and can combat infection in the tissues, ingest dead cells and assist lymphocytes in their immune functions.

Multidrug Resistance (MDR)

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

Mutation

An alteration in a gene that results from a change to a part of the stretch of DNA that represents a gene. A "germ cell mutation" is present in the egg or the sperm and can be transmitted from parent(s) to offspring. A "somatic cell mutation" occurs in a specific tissue cell and can result in the growth of the specific tissue cell into a tumor. Most cancers start after a somatic mutation. In leukemia, lymphoma or myeloma, a primitive marrow or lymph node cell undergoes somatic mutation that leads to the formation of a tumor. In these cases, the tumors are usually widely distributed when detected; they involve the marrow of many bones or involve lymph nodes in several sites, usually.

Neutropenia

A decrease below normal in the concentration of neutrophils.

Neutrophil

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

Oncogene

A mutated gene that is the cause of a cancer. Several subtypes of acute myelogenous leukemia, acute lymphocytic leukemia, lymphoma and nearly all cases of chronic myelogenous leukemia have a consistent mutated gene (oncogene).

Oncologist

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

Pancytopenia

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

Petechiae

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

Phagocytes

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

Philadelphia Chromosome (Ph Chromosome)

The name applied to the abnormality of the chromosome number 22 in the marrow and blood cells of patients with chronic myelogenous leukemia and some patients with acute lymphocytic leukemia. The abnormality reflects a shortened long arm of chromosome number 22. The observation was reported first by physicians at the University of Pennsylvania and named the Philadelphia chromosome. Since its discovery, the piece of lost chromosome has been shown to stick (translocate) to chromosome 9 in most cases. Indeed, some of chromosome 9 sticks (translocates) to chromosome 22. This is referred to as a “balanced translocation,” because virtually equal lengths of partial chromosome arms exchange position. Because chromosome 22 is a very short chromosome and chromosome 9 is a very long chromosome, the addition to chromosome 9 was less apparent than the shortening of 22 until more sensitive techniques became available. The abnormality of chromosome 22 is now usually abbreviated to “Ph chromosome.”

Platelets

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

Platelet Transfusion

The transfusion of donor platelets is frequently needed to support patients treated for acute leukemia. The platelets can be pooled from several unrelated donors and given as pooled, random-donor platelets. Platelets from about 6 one-unit blood donors are required to significantly raise the platelet count in a recipient. Sufficient platelets can be obtained from one donor by apheresis. The latter technique skims the platelets of large volumes of blood passing through the apheresis machine. The red cells and plasma are returned to the donor. The advantage of single-donor platelets is that the patient is not exposed to the different antigens on platelets from many different people and is less likely to develop antibodies against donor platelets. HLA-matched platelet transfusion can be given from a related donor with an identical or very similar HLA tissue type.

Polymerase Chain Reaction (PCR)

A technique to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be studied or determined. This technique has become useful in detecting a very low concentration of residual leukemia or lymphoma cells, too few to be seen using a microscope. The technique can detect the presence of one leukemic cell among 500,000 to one million nonleukemic cells. PCR requires a specific DNA (or RNA) abnormality or marker, like an oncogene, in the leukemic cells for its use to identify residual abnormal cells.

Red Cells

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

Refractory Disease

A term for disease that does not go into remission or improve substantially after initial treatment with standard therapy for the disease.

Relapse (Recurrence)

A return of the disease after it has been in remission following treatment.

Remission

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

Resistance to Treatment (see also Multidrug Resistance)

The ability of cells to live and divide despite their exposure to a chemical that ordinarily kills cells or inhibits their growth. Refractory leukemia is the circumstance in which a proportion of malignant cells resist the damaging effects of a drug or drugs. Cells have several ways to develop drug resistance.

Sanctuary Sites

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

Somatic Mutation

The alteration of a gene in the cell of a specific tissue. If the mutation occurs in a gene that normally controls cell growth or cell life span, referred to as a “proto-oncogene,” the mutated gene may become a cancer-causing gene, or oncogene. This change is called “somatic” to distinguish it from a germ cell mutation, which can be passed from parent to offspring. Cases of leukemia, lymphoma or myeloma are caused by a somatic mutation in a primitive marrow (blood-forming) or lymphatic system cell. If the mutation results from a major abnormality of chromosomes such as a translocation, it can be detected by cytogenetic examination. Sometimes the alteration in the gene is more subtle and requires more sensitive tests to identify the oncogene.

Spleen

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

Stem Cells (see also Hematopoiesis)

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

Stem Cell Transplantation (see also Autologous Stem Cell Infusion)

This is a technique developed to restore the marrow of patients who had lethal injury to that site. Such injury can occur because of primary marrow failure, destruction of marrow by disease or intensive chemical or radiation exposure. As first designed, the source of the transplant was the marrow of a healthy donor who had the same tissue type (HLA type) as the patient. Usually, the source was a brother or sister. Donor programs have been established to identify unrelated donors who have a matching tissue type. This approach requires screening tens of thousands of unrelated individuals of similar ethnicity.

The transplant product is a very small fraction of the marrow cells called “stem cells.” These stem cells not only reside in the marrow but circulate in the blood. They can be harvested from the blood of a donor by treating the donor with an agent or agents that cause the release of larger numbers of stem cells into the blood and collecting them by apheresis. The stem cells circulate in large numbers in fetal blood also and can be recovered from the placental and umbilical cord blood after childbirth. The harvesting, freezing and storing of “cord blood” has provided another source of stem cells for transplantation. Since blood as well as marrow is a very good source of cells for transplantation, the term “stem cell transplantation” has replaced “bone marrow transplantation” as the general term for these procedures.

If the donor is an identical twin, the transplant is called “syngeneic,” the medical term for genetically identical. If the donor is a nonidentical sibling, the transplant is called “allogeneic,” indicating it is from the same species and in practice nearly always matching in tissue type. The term “matched-unrelated” is applied to the donors recruited from large-volume screening programs searching for the rare individual who is very similar in tissue type to the patient. The important technique of harvesting patients’ marrow, freezing it and returning it to them after they have received intensive chemotherapy and/or radiotherapy for their underlying disease has been referred to as “autologous transplantation” (self), or “autotransplantation.” This term is a well-entrenched misnomer since transplantation implies transferring tissue from one individual to another. This technique would better be referred to as “autologous marrow infusion.”

Thrombocytopenia

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

Translocation

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

Transplantation (see Stem Cell Transplantation)

Tumor Suppressor Gene (Anti-oncogene)

A gene that acts to prevent cell growth. If a mutation occurs in this gene, it may make the individual more susceptible to the development of cancer in the tissue in which the mutation occurred.

White Cells

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

Resources

The Leukemia & Lymphoma Society Booklets

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The Society's Information Resource Center (IRC) provides patients, families and healthcare professionals with the latest information on leukemia, lymphoma and myeloma. Our information specialists – master's level oncology professionals – are available by phone (800.955.4572) Monday through Friday, 9 am to 6 pm (ET); via email (infocenter@LLS.org); or chat online at www.LLS.org (click on "Live Help").

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