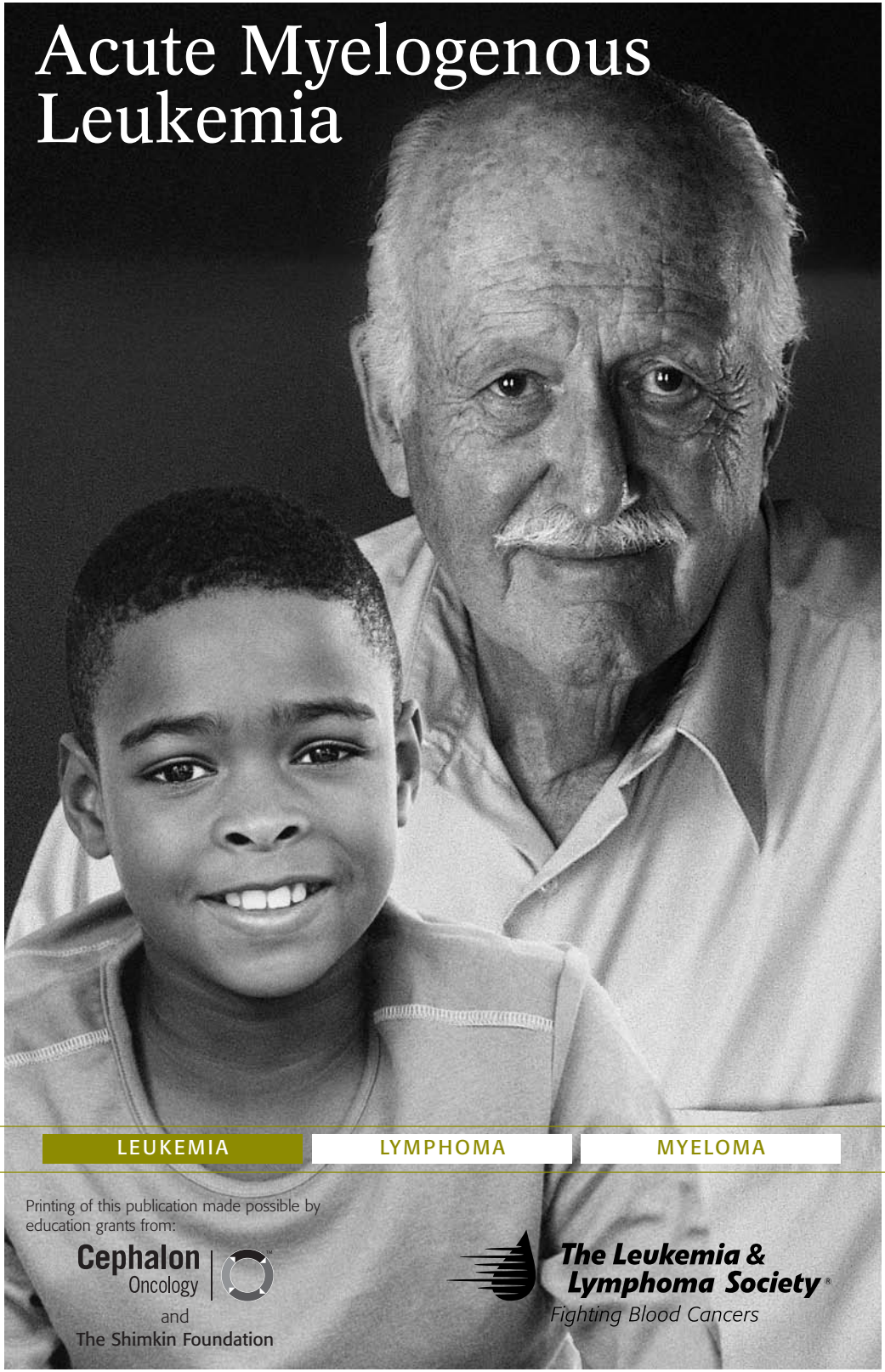
Acute Myelogenous Leukemia



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Introduction

This booklet provides information about acute myelogenous 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. We welcome comments about the information in the booklet.

About 11,920 new cases of acute myelogenous leukemia (AML) were diagnosed in the United States in 2005. (Source: Surveillance, Epidemiology and End Results [SEER] Program, 2005). Although AML can occur at any age, adults age 65 and older are more likely to develop the disease than younger people. AML accounts for about 15 to 20 percent of childhood acute leukemia cases.

Acute myelogenous leukemia may be called by several names, including acute myelocytic leukemia, acute myeloblastic leukemia, acute granulocytic leukemia or acute nonlymphocytic leukemia.

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

Normal Blood and Marrow

A brief description of normal blood and marrow is provided to help readers understand acute myelogenous leukemia-specific information that follows.

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 folic acid), and
- 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) because they can ingest bacteria or fungi and kill them. 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 in the lymph nodes, the spleen, and 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 backbones (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).

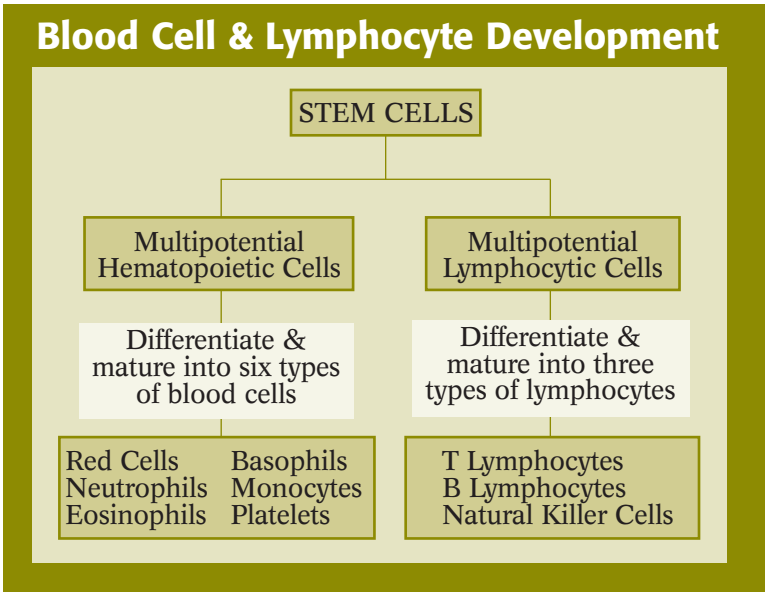


Figure 1. This simplified diagram depicts the process of stem cells developing into functional blood cells (hematopoiesis) and lymphatic cells.

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 cell counts. Their presence in the blood is important because they can be collected by a special technique and can be transplanted into a recipient if enough stem cells are harvested from a compatible donor.

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.

Leukemia

Leukemia is a cancer of the marrow and blood. The earliest observations of patients who had marked elevation of their white cells by European physicians in the 19th century led to their coining the term "Weisses Blut," or "white blood," 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 leukemia and acute or chronic lymphocytic leukemia. The term "acute lymphocytic leukemia" is synonymous with "acute lymphoblastic leukemia." The latter term is more frequently used to denote cases in children.

Acute leukemia is a rapidly progressing disease that affects mostly cells that are unformed or immature (not yet 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 more developed cells. In general, these more mature cells can carry out some of their normal functions.

The ability to measure additional specific features of cells has led to further subclassification of the major categories of leukemia. The categories and subsets allow the physician to decide what treatment works best for a given cell type and how quickly the disease may develop.

Acute Myelogenous Leukemia

Acute myelogenous leukemia results from acquired genetic damage to the DNA of a developing cell in the marrow. The effects are uncontrolled, exaggerated growth and accumulation of cells called "leukemic blasts," which 1) fail to function as normal blood cells and 2) block production of normal marrow cells, leading to a deficiency of red cells (anemia), of platelets (thrombocytopenia), and of normal white cells, especially neutrophils (neutropenia) in the blood.

Leukemia cells look somewhat like blood cells. However, the process of their formation is incomplete. When leukemia is diagnosed, the quantity of normal, healthy blood cells is insufficient (see Figure 2).

AML Blast Cells

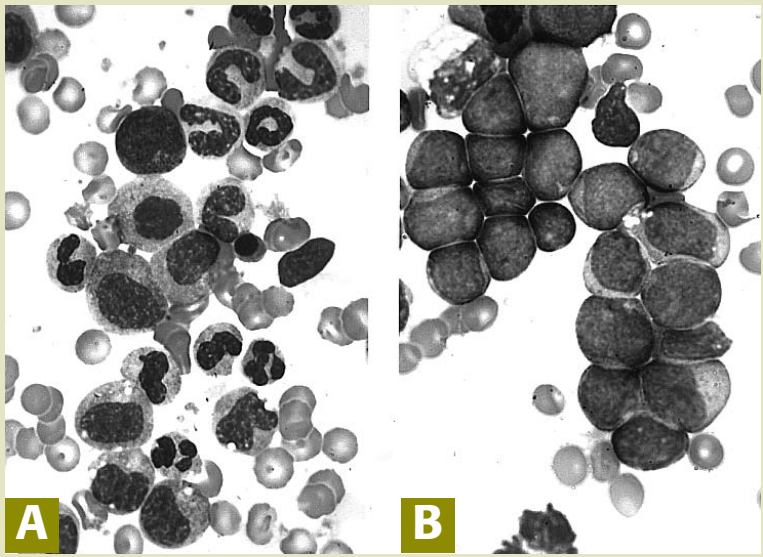


Figure 2. Panel A (on left) shows a photograph of normal marrow cells as seen through a microscope. The darker silhouettes are the nuclei of the cells. Note the differences in their shapes. Some are circular and some are horseshoe-shaped. The distinct nuclear appearances of the cells reflect their different developmental stages. Panel B (on right) shows a photograph of acute myelogenous leukemia blast cells as seen through a microscope. The consistent appearance of these cells, which are "arrested" in an earlier stage of development, is in contrast to the appearance of the normal cells shown in panel A.

Causes and Risk Factors

In most cases the cause of acute myelogenous leukemia is not known. Several factors have been associated with an increased risk of the disease. These include exposure to:

- Very high doses of irradiation, as carefully studied in the Japanese survivors of atomic bomb detonations
- The chemical benzene, usually in the workplace
- Chemotherapy used to treat cancers such as breast cancer, ovarian cancer or the lymphomas. The chemotherapy drug classes known as alkylating agents and topoisomerase inhibitors are most frequently associated with an increased risk of AML
- Therapeutic radiation, depending on the dose and duration of treatment
- Tobacco smoke

Acute myelogenous leukemia is not contagious. Uncommon genetic disorders such as Fanconi anemia, Schwachman-Diamond syndrome, Down syndrome, and others are associated with an increased risk of AML. Very rarely, an unexpectedly high number of cases of AML may be diagnosed within the same family. It is thought that offspring in these families inherit a gene that makes them more susceptible to developing AML.

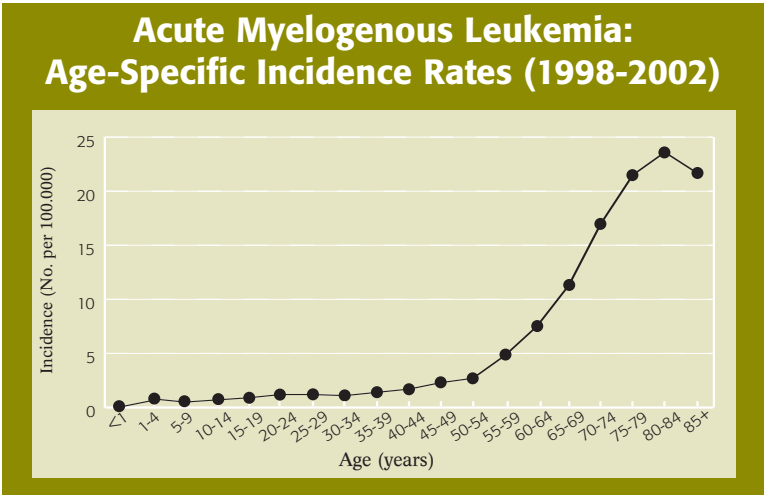


Figure 3. The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of AML per 100,000 in a given age group. (Data from the National Cancer Institute Surveillance, Epidemiology and End Results [SEER] Program, 2005.)

About 15 to 20 percent of childhood leukemias are cases of acute myelogenous leukemia. Older people are more likely to develop the disease. The risk increases about ten-fold in patients from age 30-34 (about 1 case per 100,000 people) to age 65-69 (about 1 case per 10,000 people; see Figure 3).

Subtypes of Acute Myelogenous Leukemia

The subclassification of acute myelogenous leukemia is important. Different types of therapy may be used based on subtype and the course of the disease may be different.

Physicians are aided in identifying subtypes based on seeing different types and patterns of cells in a patient's blood or marrow. These patterns are designated as the subtypes, shown in Table 1. It is possible, although uncommon, for additional subtypes to occur.

Table 1. Acute Myelogenous Leukemia Cell Subtypes

Designation	Cell Subtype
M0	Myeloblastic, on special analysis
M1	Myeloblastic, without maturation
M2	Myeloblastic, with maturation
M3	Promyelocytic
M4	Myelomonocytic
M5	Monocytic
M6	Erythroleukemia
M7	Megakaryocytic

"Myeloblast" is the term for an undeveloped type of white cell. If myeloblasts are the dominant leukemia cells in the marrow at the time of diagnosis, the leukemia is referred to as "myeloblastic" type. If there are many myeloblasts but there are some cells developing towards fully formed blood cells, the added designation, "with

maturation" is used. If there are cells that are developing features of monocytes ("monocytic" type) or red cells ("erythroleukemia" type), these designations are used, and so forth.

Most people who are diagnosed with AML have one of eight different patterns of blood cell involvement. Additional features may be important in guiding the choice of therapy, such as abnormalities of chromosomes, the cell immunophenotype, and the age and general health of the patient.

There are certain chromosomal changes that can give important information for patient management. For example, three chromosomal changes have a relatively favorable prognosis, especially in younger patients. These chromosomal changes account for between 20 to 25 percent of all cases of AML.

- AML associated with a translocation between chromosomes 8 and 21 (t8;21)
- AML associated with an inversion or translocation of chromosome 16 (t16;16)
- AML associated with a translocation between chromosomes 15 and 17 (t15;17)

AML characterized by a translocation between chromosomes 15 and 17 requires different treatment than other types of AML (see Acute Promyelocytic Leukemia Treatment on page 14).

Symptoms and Signs

Most patients with acute myelogenous leukemia feel a loss of well-being. They tire more easily, and may feel short of breath in the course of normal physical activities. They may have a pale complexion from anemia. Several signs of bleeding caused by a very low platelet count may be noticed. They include black and blue marks or bruises occurring for no reason or because of a minor injury, the appearance of pinhead-sized spots under the skin, called petechiae, or prolonged bleeding from minor cuts. Mild fever, swollen gums, frequent minor infections such as pustules or perianal sores, slow healing of cuts, or discomfort in bones or joints may occur.

Diagnosis

Blood and marrow cells are examined to diagnose the disease. In addition to findings such as lower-than-expected red cell and platelet counts, examination of the stained (dyed) blood cells with a microscope usually shows the presence of leukemic blast cells. The diagnosis is confirmed by examination of the marrow, which also shows leukemic blast cells. The blood and/or marrow cells are also used for studies of the number and shapes of chromosomes (cytogenetic examination), immunophenotyping, and other special studies, if required, such as polymerase chain reaction.

Treatment

Nearly all patients with acute myelogenous leukemia need treatment as soon after diagnosis as possible. The principal goal of treatment is to bring about a remission, in which a) there is no evidence of leukemic blast cells in the blood or marrow and b) normal blood cell production is restored and blood cell counts return to normal levels.

In most patients intensive chemotherapy is required to achieve complete remission. At least two drugs are combined to treat patients initially. Variations on standard approaches to treatment are undergoing intensive study throughout the world. Thus, a patient may receive either a different number of drugs, sequence of drugs, or types of drugs than described here and may be receiving appropriate and effective treatment. However, it is important to seek treatment in a center where physicians are experienced in the care of patients with acute leukemia.

In order to prepare the patient for chemotherapy, an indwelling catheter or port is placed in a vein in the upper chest. This is to give ready access for the infusion of drugs or blood cells and the removal of blood samples for cell counts and chemical tests.

Some AML patients may build up uric acid in their blood as a result of their very high white cell count. The use of chemotherapy may also increase uric acid, which is a breakdown product of cells. Uric acid enters the blood and is excreted in the urine. If many cells are killed simultaneously by therapy, the amount of uric acid in the urine can be so high that uric acid kidney stones can form. This may seriously interfere with the flow of urine.

Drugs such as allopurinol or rasburicase can be given to minimize the buildup of uric acid in the blood.

Chemotherapy

Induction therapy. Induction therapy is the term for the initial phase of chemotherapy treatment. In most cases an anthracycline antibiotic (e.g., daunorubicin, doxorubicin or idarubicin) is combined with cytarabine. also called cytosine arabinoside or ara-C (see Table 2). Both drugs act in different ways to prevent DNA synthesis of leukemia cells, stopping their growth and leading to their death. The anthracycline antibiotic is usually given in the first three days of treatment. Cytarabine is started at the same time but is given for seven to 10 days of treatment. Both drugs are dissolved in fluids and given to the patient via an indwelling catheter. The catheter is sometimes called a central line, a port or a Port-a-cath®.

The goal of induction therapy is to rid the blood and marrow of visible leukemic blast cells. If blast cells are still evident, a second course of chemotherapy may be required to rid the marrow of blasts. Usually the same drugs are used for each course of treatment.

When chemotherapy is effective, developing blood cells are eliminated from the marrow along with leukemia cells. This results in a severe deficiency of red cells (anemia), of phagocytes (neutropenia and monocytopenia) and of platelets (thrombocytopenia) in the blood. Transfusion of red cells, and often platelets, may be required. During this time, the deficiency of phagocytes (microbe-eating cells) permits bacteria and fungi normally present on skin in the nose, mouth or large bowel (colon), or present in the environment, to cause infection. As a result, antibiotic therapy frequently is needed to treat infection.

Normal blood cell production will return after several weeks in most patients; transfusion of cells and antibiotics no longer will be needed. Blood cell counts gradually approach normal, well-being returns and leukemia cells cannot be identified in blood or marrow. This is called a remission. In this state, residual leukemic 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 therapy in the form of chemotherapy with or without autologous stem cell infusion or allogeneic stem cell transplantation usually is advised.

Consolidation (post-remission) therapy. Since residual leukemic cells that cannot be detected in the blood or by marrow examination remain after a remission, the optimal treatment of AML usually requires additional intensive therapy after remission has been achieved. This is called consolidation therapy.

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

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

Antitumor Antibiotics

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

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

Antimetabolites

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

- 5-azacytidine (Mylosar®)
- cytarabine (cytosine arabinoside, Ara-C, Cytosar®)
- cladribine (2-Cd-A, Leustatin®)
- fludarabine (Fludara®)
- hydroxyurea (Hydrea®)
- 6-mercaptopurine (Purinethol®)
- methotrexate (Mexate®)
- 6-thioguanine (thioguanine, Tabloid®)

DNA Repair Enzyme Inhibitors

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

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

DNA Synthesis Inhibitor

This drug reacts with DNA to alter it chemically and keep it from permitting cell growth.

- carboplatin (Paraplatin®)

Cell-Maturing Agents

- all-trans retinoic acid
- arsenic trioxide (Trisenox®)

Monoclonal Antibodies

- gemtuzumab ozogamicin (Mylotarg®)

There is no consensus as to the best approach, in part because individual factors such as the age of the patient, the patient's ability to tolerate intensive treatment, cytogenetic findings, the availability of a stem cell donor and other factors may influence the approach used.

If chemotherapy is to be used, the best results occur if intensive treatment is applied. One current approach is to use very high doses of cytarabine given intravenously soon after remission occurs.

Intensive chemotherapy and autologous stem cell infusion. Therapy can be further intensified for patients who do not have an HLA-matched stem cell donor by giving very intensive chemotherapy and re-infusing the patient's own marrow or blood stem cells. Re-infusion will restore blood cell production which otherwise would be profoundly impaired by this amount of chemotherapy. The marrow or blood stem cells is harvested from the patient shortly after remission and then frozen (cryopreserved) until it is thawed for use. Special techniques are required to keep marrow cells from being damaged during the freezing and thawing process. For more information about autologous stem cell infusion, see the Society's free booklet, *Blood and Marrow Stem Cell Transplantation*.

Allogeneic Stem Cell Transplantation

Patients between the ages of approximately 1 and 50 years who are in remission and have an HLA-matched stem cell donor may be candidates for allogeneic stem cell transplantation. The decision to perform a transplant depends on the characteristics of the patient's leukemia, the age of the patient and the patient's understanding of the potential benefits and risks. For example, a younger patient with cytogenetic findings that are associated with a higher probability of relapse would be a candidate for allogeneic stem cell transplantation early in treatment. Clinical studies at several cancer treatment centers are examining strategies for performing allogeneic stem cell transplantation in older adults, utilizing less intensive, more readily tolerated preparative chemotherapy and radiation therapy. Such strategies may make stem cell transplantation available to older patients. These patients were not previously considered for such therapies due to very high rates of toxicity and mortality. (See the Society's free booklet, *Blood and Marrow Stem Cell Transplantation*.)

Acute Promyelocytic Leukemia (APL) Treatment

The treatment of the acute promyelocytic leukemia subtype of AML differs from the treatment described in the previous section. In this subtype, the cells that accumulate in the marrow can be identified as promyelocytes, the next step in blood cell formation after myeloblasts. These cells also have a specific chromosome abnormality involving chromosome number 15, usually in conjunction with chromosome 17.

A derivative of vitamin A called all-trans retinoic acid, often abbreviated as ATRA, is administered with chemotherapy. Retinoic acid is capable of inducing the leukemic promyelocytes to develop into mature cells (neutrophils). It markedly decreases the concentration of leukemic blast cells in the marrow and a remission frequently follows.

For the remission to be long-lasting, chemotherapy must then follow or it can be given concurrently. Retinoic acid often minimizes the side effects of chemotherapy because blood cell counts may be improved and the number of primitive leukemia cells is decreased by ATRA as chemotherapy is started.

Arsenic trioxide (ATO), like retinoic acid, can induce remission of acute promyelocytic leukemia. This agent has been approved for use in patients who have relapsed or are resistant to treatment with chemotherapy and ATRA.

All-trans retinoic acid and arsenic trioxide used together are being studied in APL patients who have a good prognosis. This approach does not include chemotherapy. ATRA + ATO combined with gemtuzumab ozogamycin has been used in APL patients who have a poorer prognosis. The early responses have been good but follow-up is of too-short duration to ascertain if long-term results will be equivalent to those seen in patients given ATRA and an anthracycline antibiotic (chemotherapy). Thus, studies that combine ATRA and ATO in various ways are of considerable interest and offer promise, but require further investigation.

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

AML Treatment in Children

Acute myelogenous leukemia accounts for about 15 to 20 percent of cases of acute childhood leukemias. Most cases of acute leukemia in children are acute lymphocytic (lymphoblastic) leukemia. Children are treated with a similar remission-induction regimen as adults with AML: cytarabine and an anthracycline antibiotic, such as doxorubicin or daunamycin, and often a third drug, such as mitoxantrone. This regimen is followed by a complex multi-drug program that results in about an 80 percent remission rate and about a 40 to 50 percent 5-year, relapse-free remission rate. Most of these children are considered cured. Acute monocytic leukemia and very high blast count leukemia, referred to as hyperleukocytic leukemia, are variants of AML that are much more difficult to treat, with resultant lower remission and cure rates than the average results noted above. Very young children, less than 2 years of age, also have a decreased rate of remission and cure. Certain gene abnormalities (e.g., FLT-3 mutations) and various chromosomal abnormalities (such as those involving chromosomes 5 or 7) are markers that suggest a poor outcome. Allogeneic stem cell transplantation may be used in children who have a poor prognosis or who relapse after intensive multi-drug therapy. Growth retardation, impaired intellectual development, hormone deficiencies, and heart problems may be consequences of this intense therapy in younger children. Careful, lifelong follow-up is important in long-term survivors. For more information, see the Society's fact sheet, *Long-term and Late Effects of Treatment for Blood Cancers*.

AML Treatment in Older Adults

Acute myelogenous leukemia occurs more frequently with advancing age. At least half of patients are over 65 years of age when the disease is diagnosed. Older patients are more difficult to treat and have a much poorer response to therapy for three reasons. First, the principal reason is that their leukemic cells are more resistant to therapy. The cells of older patients with AML have a much higher occurence of unfavorable chromosome abnormalities and their leukemic cells more frequently overexpress drug resistance genes as compared to younger patients. Thus, the response to therapy is usually inadequate to produce a remission or to lead to sustained remission. Second, older patients may have other medical problems, including heart, lung or kidney disease, or diabetes mellitus. The treating physician often has to select less toxic but less effective drugs or decrease the dose and frequency of treatment to avoid further compromising the patient's general health. Third, patients of advanced age, even in the absence of other medical disorders, tend to be frail and intolerant of optimal doses of chemotherapy. The drugs, doses, and frequency of treatment are often individualized to take into account the features

of the leukemia, the health of the patient, and the patient's anticipated tolerance of therapy. However, patient age alone is a limited predictor of tolerance to chemotherapy. Standardized measures of strength, reaction time, balance, and other indices, developed by experts in geriatrics, are being applied to determine the patient's physiological age. The latter measurement rather than chronological age is a better indicator of tolerance to therapy. Such determinations may permit some older patients to receive more intensive therapy, when appropriate and desired by the patient.

Special Treatments for Monocytic Leukemia

In some types of leukemia, including one subtype of acute myelogenous leukemia, monocytic leukemia, the leukemic blast cells may invade the lining of the spinal cord or brain. This does not usually occur with other types of AML. When the lining of the spinal cord or brain is involved, chemotherapy is injected into the spinal fluid. A spinal tap (lumbar puncture) is a commonly used medical procedure, performed under local anesthesia or with heavy sedation. During a spinal tap, a needle is placed into the spinal canal and the spinal fluid is removed and examined for leukemia cells. The extracted fluid volume is then replaced with fluid containing appropriate drugs, usually cytarabine or methotrexate.

Occasionally, radiation therapy may be used to treat a large, localized accumulation of leukemia cells.

Treatment Side Effects and Their Management

Acute myelogenous leukemia decreases the production of normal blood cells and the levels are further decreased by the added effects of chemotherapy. The intensity of chemotherapy required to destroy sufficient numbers of leukemia cells to permit a remission leads to even more severe decreases in red cells, phagocytes and platelets. Severe anemia, risk of bleeding due to a low platelet count, and a high likelihood of infection result. Red cell and platelet transfusions are usually effective replacements until the beneficial effects of treatment occur several weeks later and blood cell counts return toward normal. Practical methods for transfusion of phagocytes are not currently available, except occasionally in infants and very small children. In these cases antibiotic therapy is used when the earliest signs of infection develop.

A rise in temperature or chills may be the only signs of infection in a patient with a very low white cell count. Persistent coughing; tenderness at a site prone to infection, such as the area surrounding the anus or facial sinuses; sore throat; pain on urination; or frequent loose stools may also be signs of an infection. Patients, visitors and medical personnel need to wash their hands thoroughly throughout the day to decrease the risk of infection. Meticulous care of indwelling catheter sites and excellent oral hygiene, including gum care, are also important ways to reduce risk of infection.

Blood cell growth factors are used to stimulate the production of phagocytes and can shorten the time 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).

Chemotherapy affects tissues that normally have a high rate of cell turnover (also called cell division or mitosis). Thus, the lining of the mouth, the lining of the intestines, the skin and the hair follicles may be affected. As a result, mouth ulcers, diarrhea, and hair loss are common after chemotherapy. Skin rashes also may occur.

Nausea and vomiting also may be side effects of chemotherapy. These side effects result from actions both on the intestines and on centers of the brain which, when triggered, lead to vomiting. Fortunately, should nausea and vomiting occur, drugs can be given that relieve these distressing side effects in most cases.

Refractory Leukemia and Relapsed Leukemia

Some patients have residual leukemic cells in their marrow even after intensive treatment. This is referred to as "refractory leukemia." There are other patients who have a return of leukemia cells in the marrow and a decrease in normal blood cells after achieving a remission of leukemia following therapy. This situation is referred to as "relapse."

With refractory leukemia, approaches such as drugs not used in the first course of treatment or stem cell transplantation may be used in an effort to induce remission. In patients who relapse, the duration of the remission, the patient's age and the cytogenetic findings in the leukemia cells influence the approach to therapy. Drugs similar to those administered initially, different drugs, or stem cell transplantation may be used to treat the leukemia. Gemtuzumab ozogamicin (Mylotarg®), a monoclonal antibody that is coupled to a potent cell-killing agent that targets myelogenous leukemia blast cells, has been approved for treatment of older patients who have relapsed AML (see Table 2 on page 12). This agent is also being studied in combination with other drugs to treat relapsed AML.

Follow-Up

Patients who are in remission 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 required. As time progresses, the interval between assessments may be lengthened but assessment should continue indefinitely.

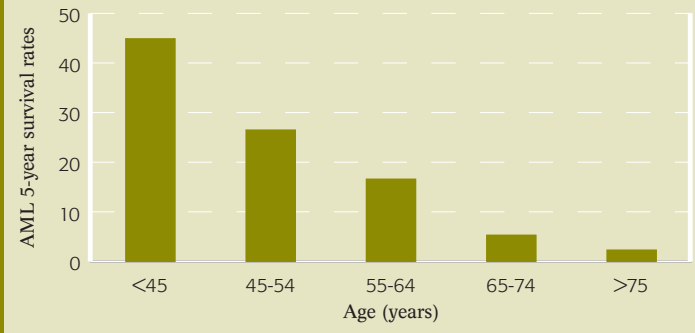
Sensitive molecular techniques permit the identification of small amounts of residual leukemia cells (minimal residual disease) at times when the blood and marrow appear normal. This approach can be used if the leukemia cells have a detectable molecular abnormality. This feature can permit more sensitive follow-up of patients who are in remission and can help determine whether additional treatment is necessary.

Outcomes. Patients with AML have one of the most difficult blood cancers to cure, although there has been progress in reaching this goal. Age is the most important determinant of cure rate. Children with the disease have a cure rate approaching 50

percent. Younger patients with certain cytogenetic patterns and with certain subtypes, such as APL, have a possibility of cure. The application of allogeneic stem cell transplantation can cure patients.

Patients diagnosed with AML before age 65 have an overall 5-year survival rate of 32.7 percent. Children under 15 years of age have an overall 5-year survival rate of 52 percent. Patients diagnosed after age 65 have an overall 5-year survival rate of 3.8 percent. The overall 5-year survival rate measured as a function of age is shown in Table 3.

Table 3. Acute Myelogenous Leukemia: Five-Year Survival Rates (1995-2000)



Source: SEER Cancer Statistics, National Cancer Institute, 2005.

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, (800) 955-4572, 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 individualized clinical trial searches for patients, family members and healthcare professionals. This service is also available on the Society's Web site, at www.LLS.org.

The proportion of patients with AML who enter remission, stay in remission for years or are cured has increased significantly over the past 30 years. Several areas of research have contributed to this progress. In children aged 2 to 10 years, the expectation of curative treatment is about 40 percent. In each succeeding decade of life, the probability of cure decreases. Cures are very infrequent in individuals after age 60 years. Since most cases occur in patients over age 50, the challenge to develop treatment programs that cure older patients (and all younger patients) must be met. Table 4 describes drugs under study for future use in AML treatment.

Table 4. Selected New Drugs in Development for the Treatment of Acute Myelogenous Leukemia

Signal Transduction Inhibitors

These drugs interfere with chemical messages within cells that cause them to survive or divide abnormally.

- Farnesyl transferase inhibitors (tipifarnib [Zarnestra®], lonafarnib)
- FLT-3 inhibitors (CEP701, PKC-412)
- Proteasome inhibitors (bortezomib [Velcade®])

Multi-drug Resistance Modulators

These drugs hinder the pump mechanism that prevents chemotherapy agents from accumulating in the cell.

- Cyclosporine A
- PSC-833

DNA Transcription Inhibitors

These drugs hinder the ability of the leukemic cell's DNA to produce the proteins that permit leukemic cell survival and propagation.

- Antisense molecules (Genasense®, GTI-2040)
- Hypomethylating agents (decitabine [Dacogen®])
- Histone deacetylase inhibitors (depsipeptide)
- Histamine dichloride (Ceplene™) and IL-2*

*These drugs are not used as frontline treatment for AML. They are being studied for maintenance of remission after induction therapy.

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 three mechanisms for drug resistance:

1) Specific genes encode proteins that probably evolved to protect the primitive cells from toxins. Examples of these proteins are P-glycoprotein (multi-drug 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 acute leukemia cells in decreasing the effectiveness of chemotherapy.

2) Gene families normally control programmed cell death, which is the pathway of action of chemotherapy. The latter induces accentuated and accelerated programmed cell death. In some blood cancers, these genes are down-regulated or blocked, thus cell death as a result of chemotherapy is blocked.

3) Specific gene families may be active in chemotherapy-resistant cells that result in relapse of the patient's leukemia. 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 multi-drug resistance. It is hoped that clinical trials of such agents may occur soon.

Oncogenes and Interacting Mutations

Understanding the precise damage (mutations) in DNA that causes a normal cell to be transformed into a leukemia cell should permit new therapies to be developed. These therapies may block the effects of cancer-causing genes (oncogenes) and the cancer-causing proteins that the genes direct to be made.

In addition to the formation of an oncogene, several gene mutations are thought to be required to cause AML. These interacting gene mutations may also be targets of therapy based on the theory that blocking an important interacting mutation would cause leukemia cell death. An example is mutations of the gene FLT-3, which can be found in the cells of about 30 percent of cases of AML. At least three drugs that interfere with the action of mutated FLT-3 are being studied in the treatment of AML.

Thus far, the results have been disappointing, but the principal of this approach is important. Success would entail a single therapy that is targeted to a key mutation in the transformation of the cell to acute leukemia. This therapy ideally should benefit a large proportion (30 percent) of patients, even though the cells of different patients were transformed in part by the action of different oncogenes. Success according to this approach would not require an agent that targets each oncogenic change in each patient's cells.

Nonmyeloablative Transplantation (Mini-Transplants)

Nonmyeloablative allogeneic stem cell transplantation is a form of transplantation therapy that may be applicable for older patients with leukemia. The conditioning therapy used for a nonmyeloablative transplant (also called a mini-transplant) is of much lower intensity than a standard stem cell transplant and does not completely inactivate the patient's immune system or treat the leukemia as intensively.

A nonmyleoablative transplant is based on two considerations: 1) much improved immunosuppressive therapy prevents the patient from rejecting the donor's stem cells, even though the patient's immune system has not been fully suppressed by the lower intensity conditioning therapy, and 2) the anticipated attack of the donor's immune cells will sucessfully supress the leukemia cells of the patient. This attack is referred to as "graft versus leukemia" or "GVL."

Over time, if successful, the donor's stem cells result in the replacement of the patient's immune system. The donor's immune cells now engrafted into the patient, recognize minor tissue antigens on the patient's leukemia cells and continue to suppress their growth.

Nonmyeloablative transplant is relatively new, and its risks and benefits have not yet been clearly established. It has benefited some patients. Thus, in patients with a matched-related donor, it may be an appropriate option for carefully selected older individuals. As is the case with allogeneic stem cell transplant in middle-aged individuals, graft versus host disease (GVHD) is an important and potentially disabling side effect of nonmyeloablative stem cell transplant.

Patients interested in exploring the possibilities of a nonmyeloablative transplant should discuss this option with their oncologist or hematologist, who can help them locate a transplant center that is investigating the procedure through a clinical trial. (Clinical trials are experimental studies designed to test a new treatment's safety and effectiveness.) To locate transplant centers performing nonmyeloablative transplants,

you can speak to your physician or contact the Society's Information Resource Center at (800) 955-4572 or www.LLS.org.

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. Then, through the method of clinical trials, they are used with patients. Researchers are also investigating new combinations of existing drugs for their usefulness in the treatment of acute myelogenous leukemia. (See Table 4 on page 20 for specific drugs.)

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. An antibody that targets myelogenous leukemia cells and carries a potent cell toxin has been approved for use by the Food and Drug Administration. Antibodies that target leukemic cells and carry a radioactive element such as isotopes of iodine or yttrium (radioimmunotherapy) have been developed and are being tested. Another approach uses vaccines made of immune cells that have been primed to attack leukemia cells.

Cytokines

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

Leukemia-Type Specific Therapy

Increasingly, clinical studies are identifying leukemia by more specific criteria than solely the appearance of the leukemia cells. These additional defining 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 cases that are likely to be unresponsive to the usual chemotherapy.

The Leukemia & Lymphoma Society has a proportion of its research funds invested in an attempt to improve the cure rate for AML. Identifying new drug targets; finding methods to overcome drug resistance; exploring ways to attack the leukemia stem cells thought to sustain the disease; developing new immune therapies, such as

vaccines; improving techniques of stem cell transplantation; and other approaches are each being supported simultaneously in our basic and applied research programs.

The strategies described above 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 cure of patients with acute myelogenous leukemia.

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 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 chance for remission bring emotional relief as the focus shifts to the treatment process ahead and the prospect of recovery.

Children's Concerns

Like adults with cancer, children with cancer may feel frightened and helpless but may be too young to fully understand their illness, its 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. Re-engaging 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 also may 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. They 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 often will cause a person to question his or her self-worth, identity, and appearance. These feelings are common and may affect one's relationships, including sexual relationships. Sexual desire may decrease for a period of time, then return. Recognition that these feelings are normal, and that many side effects are temporary, may be reassuring. Open, honest communications regarding fears and concerns can be very helpful. Your healthcare team will work toward minimizing any discomforts of treatment. Ask any questions or voice 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 booklet, *Coping: Support for People Living with Leukemia, Lymphoma or Myeloma*.

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

Allogeneic Stem Cell Transplantation (see Stem Cell Transplantation)

Anemia
A decrease in the red 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 the specific foreign substances. These foreign substances are called antigens. Plasma cells are derived from B lymphocytes. Antibodies coat, mark for destruction or inactivate foreign particles like bacteria, viruses or foreign chemicals like harmful toxins. Antibody binds specifically to its antigen. One, also, can make antibodies in the laboratory in two ways. If one injects material from one species into another, the latter will recognize it as foreign and make antibodies to it. For example, injecting human cells into rabbits allows one to prepare rabbit antibodies directed against the human cell that acted as the antigen. These antibodies are usually polyclonal antibodies. A technique known as a hybridoma can be used to get immune cells in a laboratory flask to generate a specific antibody called a monoclonal antibody. These antibodies can be used in several important ways. They can be used to identify and classify human leukemias and lymphomas or can be altered to make them useful in antibody-mediated immunotherapy.

Apheresis
The process of removing components of a donor's blood and returning the unneeded parts to the donor. The process uses continuous circulation of blood from a donor through an apparatus and back to the donor. This process makes it possible to remove desired elements from large volumes of blood. Platelets, red cells, white 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, which can be frozen, stored, and later used, instead of marrow stem cells, for transplantation.

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 is not overtly abnormal (for example, lymphoma). Technically, this procedure is not transplantation, which implies taking tissue from one individual (donor) and giving it to another person (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 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, 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, hip, 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 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 hair follicles are most sensitive to these chemicals, injury to these organs cause the common side effects of chemotherapy, i.e., 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 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 neoplasms (cancers), benign and malignant, are derived from a single cell with an injury to DNA (mutated) and, thus, are monoclonal. The mutated cell has an alteration in its DNA, which forms 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.

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, examines and interprets the number and shape of chromosomes in cells is called a cytogeneticist. In addition to identifying 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 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
A synonym for red cells (see Red Cells).

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

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

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

Growth Factors (see Cytokines)

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-sibling) the transplant (donated stem cells) are 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).

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. (See Figure 1 on page 4.)
Hematopoiesis is a continuous process that is active normally throughout life. The reason for this activity is because 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 five hundred 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, lymphoma, or myeloma cells.

Iliac Crest

The edge of the hip bone from which marrow is usually sampled for diagnosis of blood cell diseases.

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 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, which may, in turn, help 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.

Interleukin (see Cytokines)

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

A synonym for white cells (see White Cells).

Leukopenia

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

Lymph Nodes

Small structures, the size of beans, which 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 be enlarged. This enlargement of lymph nodes can be seen, felt, or measured by computed tomography (CT) scan or magnetic resonance (MR) imaging, depending on the degree of enlargement and location.

Lymphatic System

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

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 (MR) Imaging

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

Marrow (see Bone Marrow)

Monocytes (Macrophages)
A type of white cell that represents about five to ten percent of the cells in normal human blood. The monocyte, along with 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, can ingest dead cells (scavenger), and can assist lymphocytes in their immune functions.

Multidrug Resistance
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 each are determined by genes that govern how the cell will respond to the chemical agents. One type of multidrug resistance (or MDR) involves the ability to eject several drugs out of cells. The cell 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 a somatic mutation(s) 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, a type of white cell.

Neutrophil
The principal phagocyte (microbe-eating) cell in the blood. This blood cell is the main cell that combats infections. Often, it is not present in sufficient quantities in patients with acute leukemia or after chemotherapy. A severe deficiency of

neutrophils increases the patient's susceptibility to infection. A neutrophil may be called a "poly" (polymorphonuclear neutrophil) or "seg" (segmented neutrophil) because its nucleus has several lobes.

Oncogene

A mutated gene that is the cause of a cancer. Several subtypes of acute 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.

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. It requires the platelets from about six one-unit blood donors 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. The platelets are collected by apheresis.

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 five hundred thousand to one million nonleukemic cells. PCR requires a specific DNA (or RNA) abnormality or marker, like an oncogene, in the leukemic or lymphomatous 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. The 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 or progressive lymphomas.

Resistance to Treatment
The ability of cells to live and divide despite their exposure to a chemical that ordinarily kills cells or inhibits their growth. Refractory leukemia is the 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. (See Multidrug Resistance.)

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

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. (See Hematopoiesis.)

Stem Cell Transplantation

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 non-identical 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 (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 (see Autologous Stem Cell Infusion).

Thrombocytopenia

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

Translocation

An abnormality of chromosomes in marrow or lymph node cells that occurs when a piece of one chromosome breaks off and sticks to the end of another chromosome. In a balanced translocation, genetic material is exchanged between two different chromosomes with no gain or loss of genetic information. When a translocation occurs, the gene at which the break occurs is altered. This is one form of a somatic mutation that may transform the gene into an oncogene (cancer-causing) gene.

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

Further Readings

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