For more information, please contact:

or:

Home Office

1311 Mamaroneck Avenue, Suite 310

White Plains, NY 10605

Information Resource Center (IRC) 800.955.4572

www.LLS.org

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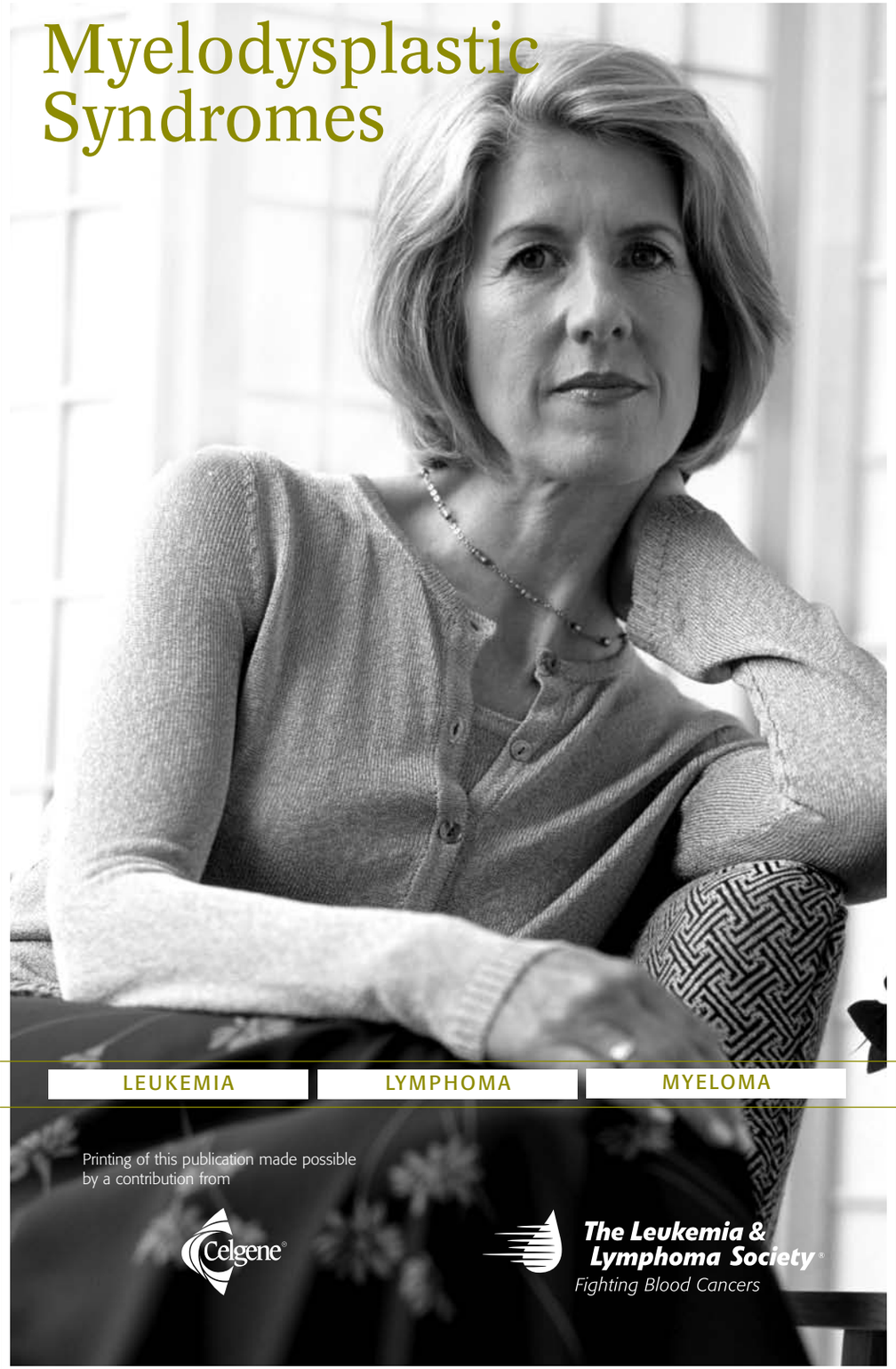
Myelodysplastic Syndromes



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Fighting Blood Cancers

Table of Contents

Introduction

The term "myelodysplastic syndromes," or MDS, has been used since the late 1970s to describe a group of blood cancers. Blood cell counts are usually low. The decrease in counts of red cells, white cells and platelets may occur to different degrees. These blood cell types also frequently have abnormalities of cell structure and function. The structural abnormalities are usually apparent in the blood examination (e.g., misshapen red cells), and these findings aid in making the diagnosis.

MDS is divided into subtypes depending on the severity of the disease. It may be nonprogressive and have little effect on a person's health and life expectancy. Even subtypes that are generally nonprogressive may result in symptomatic anemia or other problems that require treatment. Other subtypes are slower-progressing types of myelogenous leukemia that may have a serious effect on health and life expectancy.

This booklet provides information about MDS for patients and their families. We hope it is helpful and we welcome comments.

Normal Blood and Marrow

A brief description of normal blood and marrow is provided to help readers understand the MDS-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).

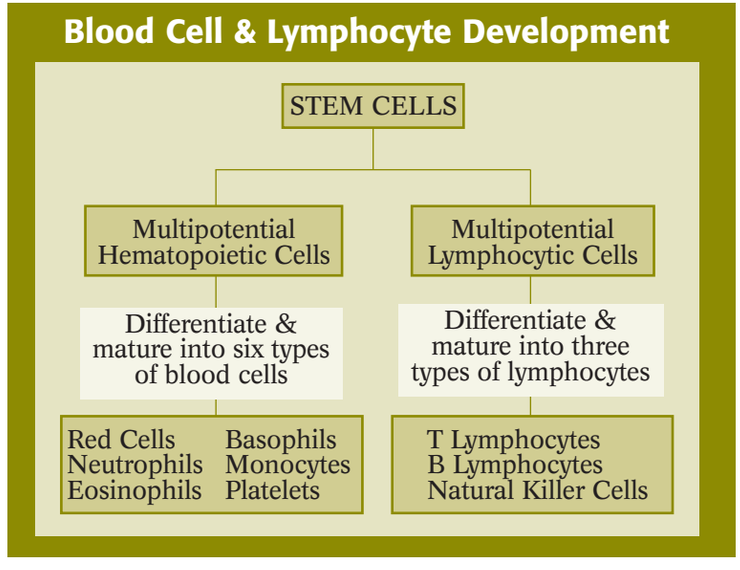

Figure 1. This figure illustrates the process of hematopoiesis, which involves the development of functional blood and lymphatic cells from stem cells. When the fully developed and functional cells are formed, they leave the marrow and enter the blood. In healthy individuals there are enough stem cells 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 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.

Myelodysplastic Syndromes (MDS)

The spectrum of diseases that are classified as MDS are each related cancers. MDS originates from mutations in a blood-forming cell in the marrow. With MDS, blood cell production in the marrow is usually exaggerated and the marrow is filled with more than the normal number of developing blood cells. This is referred to as a hypercellular marrow. The blood is usually deficient in cells. The blood cell deficiency occurs because the numerous developing cells in the marrow die as they approach maturity and before they normally would be released into the blood. Although the cells that are being formed and released into the blood are cancerous, they are so mildly affected that they often remain functional. In other words, the red cells made carry oxygen, the white cells can ingest and kill bacteria, and the platelets can plug up injury to blood vessels. In fact, a current area of investigation for MDS treatment is to devise a therapy to prevent the premature death of these cells so that they enter the blood, thus minimizing the risk of anemia, infection, or bleeding.

In more severe cases of MDS, blood cell formation is disordered in other ways; as a result, abnormal blast cells accumulate in marrow and blood. These cells do not mature into functional cells.

When there are blast cells in marrow and blood, but in lower proportions, the condition is referred to as MDS; if there are higher proportions of blast cells in the blood and marrow the disease is considered to be acute myelogenous leukemia. It is the continuum of cases of MDS – from cases without blast cells, to cases with lower proportions of blast cells, to cases with higher proportions of blast cells – that is a principal determinant of disease severity.

Incidence

The annual incidence of new cases of MDS in the United States is not known. It is believed that there is approximately the same number of new cases of MDS as the number of new cases of acute myelogenous leukemia (AML). The total estimated number of cases of AML in the U.S. for 2005 is 11,960. (Source: *Facts 2005-2006*, The Leukemia & Lymphoma Society.)

The highest incidence is in patients over 60 years of age, although people of all ages are diagnosed with MDS. The disorder is less common in children and in this population the disease is often associated with abnormal cells that have an acquired loss of chromosome 7.

Causes and Risk Factors

The causes of MDS are similar to those of acute myelogenous leukemia. In most cases the disease has no specific, clear-cut triggering event.

The following factors can increase the risk of developing MDS or acute myelogenous leukemia:

- The use of certain drugs that damage DNA. These drugs are used to treat lymphoma, myeloma, or other cancers, such as breast or ovarian cancer.
- The use of therapeutic radiation for lymphoma.
- Exposure to benzene above threshold levels for protracted periods of time, usually in an industrial setting. The stringent regulation of benzene use in the workplace has diminished the frequency of this risk factor and its potential for these consequences.

Range of Severity

The severity of MDS is varied and the marrow cell disturbance can range from mild to very severe.

Thus, the disease may be characterized as:

- Chronic or indolent (non- or very slowly progressive) and be evident primarily as mild to moderate anemia.
- Having severe decreases in red cells, white cells and platelets, and more troublesome.
- Having severe decreases in blood cells and the presence of leukemic blast cells in the marrow and blood, and even more threatening to the health of the patient.

In addition, the disease can progress such that the leukemic blast cells take over the marrow and the disease evolves into acute myelogenous leukemia. In this case, the marked decrease in blood cell formation makes it difficult for patients to prevent or fight infection and it predisposes them to exaggerated bleeding. (See the Society's free booklet, *Acute Myelogenous Leukemia*.)

Diagnosis

A diagnosis is made by measuring a person's blood cell counts and examining the appearance of the blood cells in blood and marrow under a microscope. In addition, a sample of blood and marrow cells is examined to determine if there are any chromosomal abnormalities. This examination of cells, called a cytogenetic analysis, can be helpful in reaching a conclusion about the diagnosis. The marrow cells are obtained through tests called bone marrow aspirate and bone marrow biopsy.

Fluorescence (F) in (I) situ (S) hybridization (H), often referred to as FISH, is a method to identify cells whose nuclei contain chromosomal abnormalities. FISH can be used to identify abnormal cells for diagnosis and to follow the effects of therapy.

Disease Subtypes

Although myelodysplastic syndromes cover a spectrum of diseases (see Table 1 below), most cases can be placed into one of several subtypes based on the patient's blood cell counts and the appearance of blood cells under the microscope.

Table 1. Myelodysplastic Syndrome Subtypes

Acquired refractory anemia (*clonal anemia*)
Acquired refractory sideroblastic anemia (*clonal sideroblastic anemia*)
Pancytopenia with hyperplastic marrow (*clonal pancytopenia*)
Refractory anemia with excess blasts (*oligoblastic myelogenous leukemia*)

Descriptions of the MDS subtypes above are provided in the text or glossary.

The two principal subgroups are 1) chronic or nonprogressive forms of MDS, and 2) progressive and symptomatic forms of MDS.

Chronic or Nonprogressive Forms of MDS

Refractory Anemia. Blood cell count deficiencies with no sign of leukemic blast cells make up about one-third of the myelodysplastic disorders. The disorder may cause principally a deficiency of 1) red cells, 2) red cells and white cells, or 3) red cells, white cells and platelets.

These cases are often referred to as "refractory anemia," even though white cell and platelet counts may be low along with red cell counts. "Pancytopenia" is the term that may be used when there is a decrease in the concentration of red cells, white cells and platelets.

Refractory anemia may be nonprogressive for years or decades. If the blood cell count deficiencies are mild, the condition may have little effect on the patient's ability to conduct his or her usual activities. About ten to fifteen percent of patients in this subgroup may later develop acute myelogenous leukemia.

Refractory Sideroblastic Anemia. A special feature, abnormal sideroblasts, may be present in the developing red cells in the marrow. In such cases, the disease is often referred to as "refractory sideroblastic anemia" or "acquired sideroblastic anemia." "Sidero" is a prefix meaning "iron." All normal developing red cells contain fine particles of iron that are incorporated into hemoglobin, the oxygen-carrying protein that gives red cells their color and function. In the case of abnormal sideroblasts, large quantities of iron are trapped in the developing red cells in abnormal sites. Staining marrow cells for iron and examining them under the microscope can identify these cells as abnormal sideroblasts.

Some patients with chronic forms of MDS may have blood count abnormalities, such as anemia, that create symptoms and may require treatment.

Progressive and Symptomatic Forms of MDS

Refractory Anemia with Excess Blasts. The second principal subtype of myelodysplastic disease shows evidence of leukemic blast cells in the marrow. This finding is associated often with low red cell, white cell and platelet counts, and other changes of blood cell shape and structure under the microscope. This subtype has been called "low blast count myelogenous leukemia," "refractory anemia with excess blasts," "smoldering leukemia," and "oligoblastic myelogenous leukemia."

It has a wide range of severity. The rate of progression of this second subtype correlates with the proportion of leukemic blast cells in the marrow and the degree of the abnormalities in blood cell counts.

Signs and Symptoms

Chronic or Nonprogressive Forms of MDS. The diagnosis of chronic or nonprogressive MDS may be suspected from a finding of anemia during a medical evaluation. If the anemia is moderate or severe, exaggerated fatigue, shortness of breath on exertion (such as during climbing stairs), pale skin or weakness may be present. In this form of the disease, abnormalities that may be present in white cells or platelets are usually insufficient to contribute to signs or symptoms.

Progressive and Symptomatic Forms of MDS. In the more advanced and progressive form of the disease (low blast cell count myelogenous leukemia) the patient often needs medical attention because of:

- Loss of a sense of well being
- Fatigue
- Weakness
- Loss of appetite
- Occasionally, skin bleeding, also called purpura, and prolonged bleeding from cuts as a result of very low platelet counts.
- Skin, sinus or urinary tract infections or infections in other sites because of low white cell counts.

In general, recurrent, serious infections are not usually prominent at the time of onset.

Disease Progression

The subtypes of MDS that result in anemia (low red cell count), and sometimes slight or moderate decreases in white cell or platelet counts, may be stable for decades without dramatic health consequences. Other cases that are characterized by very low blood cell counts (severe cytopenias), and the presence of leukemic blast cells, usually result in serious problems related to severe anemia, and sometimes exaggerated bleeding and recurrent infections. Each group may progress to more full-blown myelogenous leukemia, but this occurs more frequently and sooner in the more severe types of myelodysplastic syndromes.

The likelihood of disease progression is defined in two ways:

1. By subtype of MDS: Table 1, on page 7, lists the names of the various subtypes of MDS in order of the increased likelihood of progression to acute myelogenous leukemia (AML).
2. By International Prognostic Scoring System: (see below), which assigns the disease into one of four categories, indicating risk of progression toward acute myelogenous leukemia.

The two classification schemes mentioned above are closely correlated. Common features of the MDS subtypes include:

- A tendency toward changes in cell structure that are visible using the light microscope. These changes in size and shape of red cells and alterations in the appearance of white cells and platelets can be appreciated through the microscope and are helpful in diagnosis.
- Often, low red cell, white cell and platelet counts.
- Presence of lower proportions of leukemic blast cells.

The International Prognostic Scoring System

The International Prognostic Scoring System (IPSS) was devised in order to translate a patient's degree of disease severity for a particular type of myelodysplastic disease from broad descriptions into an objective standard. The IPSS can be used to predict the risk of progression of the disease if untreated. The IPSS converts the three factors below into a numerical score that is stratified into four categories of risk of progression toward AML:

1. The severity of chromosome changes in the marrow cells.
2. The percentage of marrow leukemic blast cells.
3. The presence of one or more cytopenias, e.g., anemia, anemia and low white cell counts, or anemia, low white cell counts, and low platelet counts.

The four categories of risk of progression toward AML are:

- Low risk
- Intermediate-1 risk
- Intermediate-2 risk
- High risk.

The IPSS also is useful in interpreting the results of cooperative clinical trials involving patients at different treatment centers. These scores are useful but must be integrated with the actual observations of an individual patient since the IPSS is not a precise predictor of progression.

If treatment is needed, there are three general approaches:

- Supportive care (e.g., transfusions and cytokines)
- Lower-intensity therapy (one or two drugs, such as azacitidine, decitabine or lenalidomide)
- Higher-intensity therapy (e.g., intensive AML chemotherapy or stem cell transplantation).

Treatment: Determining Need and Treatment Approaches

When MDS is diagnosed, the physician sometimes recommends watchful waiting. In the group of MDS diseases, those patients at the stable or indolent end of the spectrum are often not treated. Patients who have stable forms of myelodysplastic syndrome, such as mild refractory anemia with mild to moderate decreases in white cell and platelet counts, may not require treatment and their usual activity levels are little affected.

It is important to have a physician who is familiar with the disease to evaluate the patient and monitor his or her blood cells periodically. It is possible to have little change in status for years or decades. However, since there is a risk of progression to a more severe disturbance in blood cell formation, which in the extreme is acute myelogenous leukemia, periodic surveillance is important.

In patients who have more severe problems, treatment to improve blood cell counts may lead to alleviation of symptoms. Curative therapy is not available for most patients at this time. Younger individuals who are candidates for allogeneic stem cell transplantation may have restoration of normal blood cell formation after a successful transplant.

Supportive Care

In patients with more troublesome decreases in blood cell counts, drugs that can stimulate blood cell production may be useful. Erythropoietin and granulocyte-colony stimulating factor (G-CSF) used in combination can increase the red cell count and sometimes the white cell count in some patients. Other cytokines are being studied to increase the platelet count, if necessary. Cytokine therapy is more useful in patients in lower risk categories. These approaches work in some but not all patients and, if necessary, periodic red cell or platelet transfusion therapy may be required. The Society's free booklet, *Blood Transfusion*, provides comprehensive information on transfusion of red cells, white cells, platelets and other blood components for patients with MDS and other blood cancers.

Prompt attention to infection or unexplained fever is also important. Where bacterial or fungal infections are identified or suspected, appropriate antibiotics may be needed. Antiviral drugs may be used to treat certain viral infections.

Lower-Intensity Therapy

Numerous single-drug approaches are in practice or are being studied. Some approaches that are commonly used are:

- Azacitidine (Vidaza®), a drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of all MDS subtypes, which included both low- and high-risk patients. This drug appears to help the bone marrow of a person with MDS begin to function more normally. It also kills the unhealthy cells in bone marrow that have been reproducing abnormally. On average, about 40% of patients respond to azacitidine.
- Lenalidomide (Revlimid®), to improve low blood cell counts. This is an FDA-approved drug for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality, with or without additional abnormalities. A deletion involving the 5q chromosome may be involved in 20% to 30% of all MDS cases. Studies have shown that Revlimid® reduced the need for red cell transfusion, increased hemoglobin and eliminated dysplastic cells.
- Decitabine (Dacogen®), a drug being studied in clinical trials for patients with MDS. See *Clinical Trials* on page 14.

Higher-Intensity Therapy

In more severe and progressive cases, the disease may require treatment with cytotoxic drugs. This form of treatment, chemotherapy, is planned depending on:

- The age and coexisting medical conditions of the patient,
- The severity of the manifestations of the disease, and
- The rate of progression of the disease.

Drugs that may be used are:

- Cytosine arabinoside or ara-C (Cytosar-U®)
- Idarubicin (Idamycin®)
- Daunorubicin (Cerubidine®) or
- Mitoxantrone (Novantrone®).

The drugs may be given alone or in a combination of two or three different agents (combination chemotherapy). In some cases, low-dose programs are used. More information about these drugs is in the Society's free booklet, *Understanding Drug Therapy and Managing Side Effects*.

Initially, the application of chemotherapy will make the cell counts worse. Thus, the physician has to assess whether intensive chemotherapy is warranted due to the severity of the cell disturbances and the possibility that the patient has a reasonable chance of responding to the initial cytotoxic phase of therapy with a remission.

In the small proportion of patients who:

- are under 50 years of age
- have a severe form of myelodysplastic syndrome, and
- have an appropriate stem cell donor

intensive radiation and/or chemotherapy followed by allogeneic stem cell transplantation, can be considered as potentially curative therapy.

Nonmyeloablative allogeneic transplantation clinical trials are underway to determine the usefulness of this approach in older patients. (See the *Clinical Trials* section of this booklet.)

Table 2. Types of Therapy for Myelodysplastic Syndromes

Cytokines
(e.g., epoetin alfa, darbepoetin alfa and granulocyte-colony stimulating factor (G-CSF))

Single agents
(e.g., azacitadine, decitabine, lenalidomide)

Multiple agents
(e.g., cytarabine and daunrubicin, cytarabine, idarubicin, mitoxantrone and thalidomide)

Stem cell transplantation
(e.g., allogeneic, nonmyeloablative allogeneic)

Clinical Trials: New Drugs or New Applications of Drugs

It is anticipated that new drugs, drug combinations and other therapies will prove useful in MDS treatment. The following therapies are among those under study:

- Decitabine (Dacogen®)

  Decitabine is similar to azacitidine (Vidaza®), which was approved for MDS treatment by the FDA in May 2004. Phase II decitabine clinical trials for MDS treatment were reported to show favorable response in platelet counts of patients. A Phase III trial of decitabine compared patients receiving decitabine plus supportive care to patients receiving supportive care only. Overall patient response (partial or complete) to decitabine was reported to be 22%.

- Arsenic trioxide (Trisenox®)

  This drug is used principally to treat acute promyelocytic leukemia and may be useful in treating MDS. Preliminary data from clinical studies indicate that arsenic trioxide has clinical activity as a single agent in MDS, and combination therapies are being investigated.

- Farnesyl transferase inhibitors, e.g., tipifarnib (Zarnestra®), lonafarnib (Sarasar®)

  Farnesyl transferase inhibitors (FTIs), a new class of drug therapy, are being considered in the treatment of several blood cancers including acute myelogenous leukemia (AML), especially in older patients and in MDS. FTIs are being evaluated as a single agent and in combination with other drugs.

- Nonmyeloablative allogeneic stem cell transplantation

  Studies of nonmyeloablative allogeneic stem cell transplantation are underway to determine the usefulness of this approach in older patients. Patients being conditioned for a nonmyeloablative transplant receive lower doses of chemotherapy drugs and or radiation in preparation for the transplant. Immunosuppressive drugs are used to prevent rejection of the graft and the engraftment of donor immune cells may allow these cells to attack the disease (graft versus cancer effect).

Social and Emotional Aspects of MDS

Living with a serious disease is a challenge. Patients may need to make lifestyle changes, which can be distressing. MDS also places a strain on family members and friends. Talking to the physicians, nurses and social workers on your healthcare team may help ease concerns about the disease and the future. The professional staff is also prepared to offer referrals to other resources. Many patients feel emotional relief once they can reestablish a sense of control in their lives. The following information may assist in the management of common health problems for patients with the disease.

The diagnosis of a myelodysplastic syndrome may provoke a profound emotional response in patients, family members and friends. Denial, depression, a feeling of hopelessness, and fear are normal and usual reactions. 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, 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.

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 providers 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 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 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 stress 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

Acute Myelogenous Leukemia (AML)
A progressive cancer that starts with the malignant transformation of an immature cell in the marrow. The affected cell usually is a primitive multipotential cell, meaning that its normal counterpart can give rise to a variety of blood cell types. The transformed cell multiplies and accumulates in the marrow as leukemic myeloblasts. Other terms that are synonyms for AML include acute non-lymphocytic leukemia, acute myeloid leukemia, and acute myelocytic leukemia. (See the Society's booklet *Acute Myelogenous Leukemia*.)

Allogeneic Stem Cell Transplantation
The transfer of stem cells between two people, where the donor and the recipient are not identical twins. An effort is made to find a donor who is very similar in tissue type to the recipient by matching their HLA types. The closer the similarity, the higher the probability that harmful immune reactions will be minimized and the transplant will be a success. Siblings are the most likely to be closely matched, but other family members and unrelated matched donors can be similar enough to achieve a successful transplant if the optimal match is not available and the severity of the illness justifies the risk. In the treatment of blood cancers, the cells to be transplanted are pluripotential stem cells, but they are mixed with other marrow or blood cells when infused. (See the Society's booklet *Blood and Marrow Stem Cell Transplantation*.)

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

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, 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 booklet *Blood and Marrow Stem Cell Transplantation*.)

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 lymphoblastic 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.

Blood Cells

There are three main types of cell in the blood: red cells that carry oxygen, white cells that principally prevent or combat infections, and platelets that help prevent bleeding. There are several types of white cells in the blood. Each cell type is represented in blood in the numbers that meet the functions they serve. One fluid ounce of blood contains about 150 billion red cells, 8 billion platelets, and 20 million white cells. Red cells live for months, platelets for a week or two, and white cells for a few days. The marrow must replace over 200 million cells removed from the blood each day.

Blood Count

A laboratory test requiring a small blood sample with which to measure the number and types of cells circulating in the blood. The term "complete blood count" or "CBC" is often used to refer to this test. (See the Society's fact sheet, *Understanding Blood Counts*.)

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 Aspirate and Biopsy

In this procedure, a small volume of bone marrow is removed under local anesthesia from either the hipbone (pelvis) or breastbone (sternum). The cells in the sample are placed on a glass slide, stained, and examined under the microscope to identify any abnormality in the developing blood cells. Marrow cells may also be used to immunophenotype cells and to study their chromosomes. A trephine biopsy may be taken at the same time. In this procedure a core of bone with enclosed marrow is removed with a special needle. The specimen is treated to soften the bone, then is fixed in preservative, sectioned into thin slices, stained and examined under the microscope.

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 normal cells of the marrow, the intestinal tract, the skin and hair follicles are most sensitive to these chemicals, injury to these organs cause the most common tissue effects of chemotherapy, i.e., low blood cell counts, mouth sores, diarrhea, 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 accounts for 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 an Y chromosome in males. The number or shape of chromosomes may be altered in lymphoma or leukemia cells.

Clinical Trial

A carefully planned study of a new drug or treatment approach or a new application of an existing drug or approach. In a Phase I trial, a new agent that has been tested on cells and then animals in the laboratory is examined in a relatively small number of volunteers, often with advanced disease and poorly responsive or unresponsive to existing treatment, to assess dosages, patient tolerance, and acute toxic effects. If efficacy is evident, the new approach may be tested in a Phase II trial in which more patients are studied and more information is gathered on dosage, effects, and toxicity. In a Phase III trial, the drug or drugs or new approaches are compared in patients who are randomized to receive the current existing best treatment or the new treatment. Larger numbers of patients are studied. An effort is made to minimize observer bias. Careful analysis of results is performed. Such trials are required to gain the information required by the Food and Drug Administration to determine efficacy and safety before approving a drug for marketing. Federal guidelines for informed consent of participants must be followed.

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 cancers that are monoclonal, that is, derived from a single malignant cell.

Clonal Anemia or Clonal Pancytopenia

Terms that may be used instead of “acquired” or “refractory” anemia. The terms “acquired” and “refractory anemia” do not indicate the malignant (cancerous) nature of these disorders or convey their position in the spectrum of myeloid leukemia. In modern terms, a clonal disorder is the signature feature of cancer.

Conditioning Treatment

Intensive therapy of a patient with cytotoxic drugs or drugs and total body radiation just before receiving a stem cell transplant. The therapy serves three purposes. First, it severely depresses the lymphocytes that are the key cells in the recipient’s immune system. This action helps to prevent the rejection of the graft. Second, it markedly decreases the marrow cells, which may be important to open up the special niches that are where the transplanted stem cells must lodge to engraft. Third, if the patient is being transplanted for a malignancy, this intensive therapy serves to greatly decrease any remaining tumor cells.

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-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.”

Cytopenia

A reduction in the number of cells circulating in the blood.

Cytotoxic Drugs

Anti-cancer drugs that act by killing or preventing the division of cells.
(See Chemotherapy.)

Deletion
A chromosome abnormality in which part or all of a single chromosome has been lost.

DNA
The abbreviation for deoxyribonucleic acid. This nucleic acid provides the mechanism for storing genetic information. There are four different chemical components of DNA, called bases, that are arranged in various sequences. The four bases are abbreviated C, A, T, and G. Long sequences of these four bases form a gene, and the base sequence carries the code that determines the protein that will be made as a result of the action of that gene. The genes determine an individual's inherited characteristics.

Erythropoetin (EPO)
A hormone that is required for the normal production of red cells. It is produced mainly by the kidneys and is released into the blood in response to decreased levels of oxygen in the blood. Epoetin alfa (Epogen®, Procrit®) and darbepoetin alfa (Aranesp®) are laboratory-made forms of the human hormone erythropoietin that can be used to treat anemia. In oncology, these drugs are used to assist in the recovery from chemotherapy-induced anemia or to treat chronic diseases in which anemia is a troublesome finding, such as lower-risk MDS. These drugs stimulate red blood cell production by the same mechanism as EPO, that is, by interacting with the EPO receptor on red cell progenitors.

Fluorescence In Situ Hybridization (FISH)
This test is used to detect chromosomal abnormalities. FISH studies can be used on either blood or marrow cells and do not require that the cells be in a specific phase of cell division, as is the case in other tests for chromosomal abnormalities. The ability to examine blood cells obtained by routine procedures simplifies the process for the patient. To do the test, a laboratory chemical probe is established for the chromosomal abnormality of interest. The probe binds (hybridizes) to the site of interest on the chromosome and can be identified by a color-coded fluorescent tag, e.g., a red or green tag, attached to the probe. This test can be used to identify abnormal cells for diagnosis and to follow the effects of therapy.

Graft Rejection
Rarely, when a patient has an allogeneic stem cell transplant, the donor stem cells will fail to sustain blood cell production because the recipient's lymphocytes attack the donor stem cells. The conditioning of patients with cytotoxic therapy before transplantation is intended to suppress the recipient immune system sufficiently to avoid rejection of the graft. In occasional recipients, a graft may not be successful because too few donor cells are infused.

Granulocyte-Colony Stimulating Factor (G-CSF)
A cytokine that stimulates the production of neutrophils (a type of white cell) 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."

Hemapheresis
The process of removing a donor's blood to extract a specific component 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 a platelet transfusion from one donor (rather than six to eight separate donors). In so doing, the recipient of the platelets is exposed to the blood of 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 that can be frozen, stored, and, later, used instead of marrow stem cells for transplantation. The system of hemapheresis is closed and sterile.

Hematocrit
The proportion of the blood occupied by the red cells. Normal values are 40-54 percent in males and 35-47 percent in females. If the hematocrit is below normal, one has anemia. If the hematocrit is above normal, one has erythrocytosis.

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.

Hematology
The study of blood diseases, including leukemia, lymphoma and myeloma.

Hemoglobin
The iron-containing pigment in red cells that carries oxygen to the tissue cells. A reduction in red cells decreases the blood hemoglobin. A decreased blood hemoglobin concentration is called "anemia." The decrease in hemoglobin concentration decreases the oxygen-carrying capacity of blood. If severe, this decreased capacity may limit a person's ability to exert himself or herself. Normal values of blood hemoglobin are 12 to 18 grams per 100 ml of blood. Healthy women have on average about 10 percent less hemoglobin in their blood than men do.

Indwelling Catheter
Several types of catheters (e.g. HICKMAN®, BROVIAC®, 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, nutritional 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.

Oligoblastic Myelogenous Leukemia
A term that more accurately describes the nature of the disorder referred to as "refractory anemia with excess blasts." The latter name is commonly used to designate a type of myelodysplastic syndrome that displays overt evidence of leukemic blast cells on examination of the blood or marrow. The proportion of blast cells in the marrow may be small but sufficient to indicate that leukemic hematopoiesis is present. The term "smoldering leukemia" has also been used for this manifestation but the implication of very slow progression is not always the case.

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

Opportunistic Infection
The term applied to infections with bacteria, viruses, fungi, or protozoa to which individuals with a normal immune system are not usually susceptible. These organisms take advantage of the opportunity provided by immunodeficiency. Immune deficiency can be acquired as a result of cancers of the lymphatic system such as chronic lymphocytic leukemia or myeloma, can be induced or made more severe in patients who require intensive, prolonged chemotherapy or radiotherapy, can result as a consequence of infection with the human immunodeficiency virus (HIV), and can occur as a sequel to allogeneic stem cell transplantation and severe graft-versus-host disease.

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.

Platelet Transfusion
The transfusion of donor platelets may be required to treat or prevent bleeding in patients treated with high-dose chemotherapy or radiotherapy who develop severe platelet deficiency. The platelets can be pooled from several unrelated donors and given as "pooled random-donor platelets." It requires the platelets from at least six one-unit blood donors to significantly raise the platelet count in a recipient. Sufficient platelets can be obtained from one donor by hemapheresis. The latter technique skims off the platelets of large volumes of blood passing through the hemapheresis 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 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 hemapheresis.

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."

Purpura
The presence of skin bleeding. This may be in the form of black and blue patches of varying sizes (ecchymoses) or pinhead-sized spots called petechiae, or both.

Red Cells
Blood cells that contain hemoglobin. Hemoglobin binds oxygen when red cells pass through the lung and releases it to the tissues of the body. The red cells make up a little less than half the volume of blood in healthy individuals.

Refractory Anemia
A clonal myeloid disorder that primarily affects red cell production in the marrow. In some cases the developing red cells have an abnormal accumulation of iron granules around the nucleus. These cells are called "ringed sideroblasts." Refractory anemia (RA) and refractory anemia with ringed sideroblasts (RARS) are often associated with mild to moderate decreases in white cells and platelets. These disorders are also referred to as "myelodysplasia."

Refractory Anemia with Excess Blasts
A clonal myeloid disorder characterized by the marrow and blood features of refractory anemia but with overt leukemic myeloblasts evident in the marrow and sometimes the blood. Usually the marrow blast cell proportion is between two and twenty percent. The disorder is also referred to as oligoblastic (low blast count) leukemia. The disease is less rapidly progressive than florid acute myelogenous leukemia but often evolves into a more acute leukemia.

Relapse or 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.

Risk Factor
A factor that is scientifically established to increase a person's chance of getting a disease. Risk factors can be classified as either genetic (inherited), lifestyle-related, or environmental. The presence of one or more risk factors does not mean that a person will necessarily develop the disease. In the case of environmental exposure, extent of exposure and duration are important considerations in determining if risk is increased.

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 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.

Stem Cell
These are primitive cells in marrow that are required to make red cells, white cells and platelets (see definition for Hematopoiesis). 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

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 cells of a healthy donor who had the same tissue (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 also 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 a release of larger numbers of stem cells into the blood and collecting them by hemapheresis. 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" provides 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 donor recruited from large-volume screening programs searching for the rare individual who is very similar in tissue type to the patient. (See also Autologous Stem Cell Infusion).

Thrombocytopenia

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

White Cells

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

Resources

Nontechnical Sources

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Other Resources

The Leukemia & Lymphoma Society
Contact the Information Resource Center
Phone: (800) 955-4572
Contact your local Society chapter online to find Society resources near you.
Internet address: www.LLS.org

NIH/National Cancer Institute
Internet address: www.cancer.gov
Phone: (800) 422-6237, 9:00 a.m. to 4:30 p.m. ET, Monday through Friday. TTY (800) 332-8615 or e-mail cancergovstaff@mail.nih.gov.

Marshall A. Lichtman, M.D., Executive Vice President for Research and Medical Programs of The Leukemia & Lymphoma Society, contributed the material presented in this booklet.

Notes

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