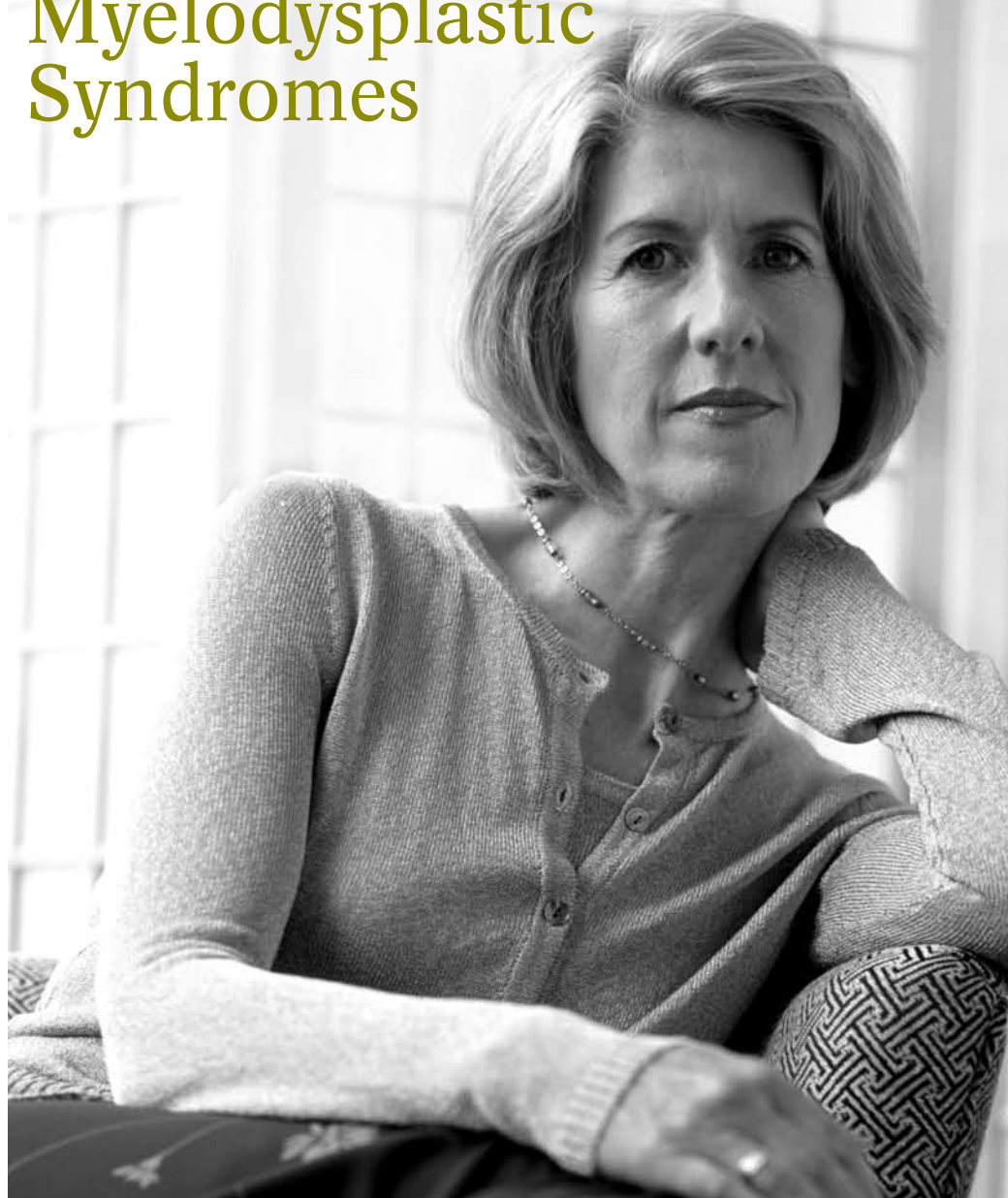


Myelodysplastic Syndromes



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Introduction

This booklet provides information about myelodysplastic syndromes (MDS) for patients and their families. About 10,268 cases of MDS were reported in the United States between 2001 and 2004 (source: Surveillance, Epidemiology, and End Results [SEER] Program, 2001-2004, National Cancer Institute, 2007). However, some researchers estimate that the numbers may actually be much higher.

The term “myelodysplastic syndromes,” or MDS, has been used since the late 1970s to describe a group of diseases of the blood and marrow, with varying degrees of severity, treatment needs and life expectancy.

This booklet begins with a brief description of normal blood and marrow, provided for background, followed by a detailed description of MDS and its treatment. It includes a glossary to help readers understand medical terms. Some of the medical terms used throughout this booklet may be synonyms for other words or phrases used by healthcare professionals. For example, MDS has been known as “smoldering leukemia,” “preleukemia” or “oligoleukemia.” Check with your physician if you have questions about how the terms used in this booklet apply to you. We hope this information is of assistance, and we welcome comments about the booklet.

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

Normal Blood and Marrow

An essential role of the bone marrow is to produce red cells, white cells and platelets. Each day, the bone marrow releases many millions of these cells into the blood to replace older cells that are removed from the blood. Diseases of the blood and marrow, such as MDS result in reduced numbers of red cells, white cells and platelets.

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; antibodies, including those developed by the body after vaccination (such as poliovirus antibodies); and clotting factors
- Hormones, such as thyroid hormones
- Minerals, such as iron, calcium, magnesium, sodium and potassium
- Vitamins, such as folate and B₁₂.

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

- The red cells make up about 40 to 45 percent of the blood. They are filled with hemoglobin, the protein that picks up oxygen in the lungs and delivers it to the cells all around the body.
- The platelets are small cell fragments, one-tenth the size of red cells, which help stop bleeding at the site of an injury in the body. For example, when a person gets a cut, the vessels that carry blood are torn open. Platelets stick to the torn surface of a 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 (also called “polymorphonuclear leukocytes,” “PMNs” or “polys”) and monocytes are white cells. They are called “phagocytes” (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 organisms 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 the lymphatic channels, but some enter the blood. There are three major types of lymphocytes: T cells, B cells and natural killer cells. These cells are a key part of the immune system.

Marrow is a spongy tissue where blood cell development takes place. It occupies the central cavity of bones. In newborns, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have functioning marrow. The back bones (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.” The stem cells, a small group of cells, develop into all the blood cells in the marrow by the process of differentiation (see Figure 1).

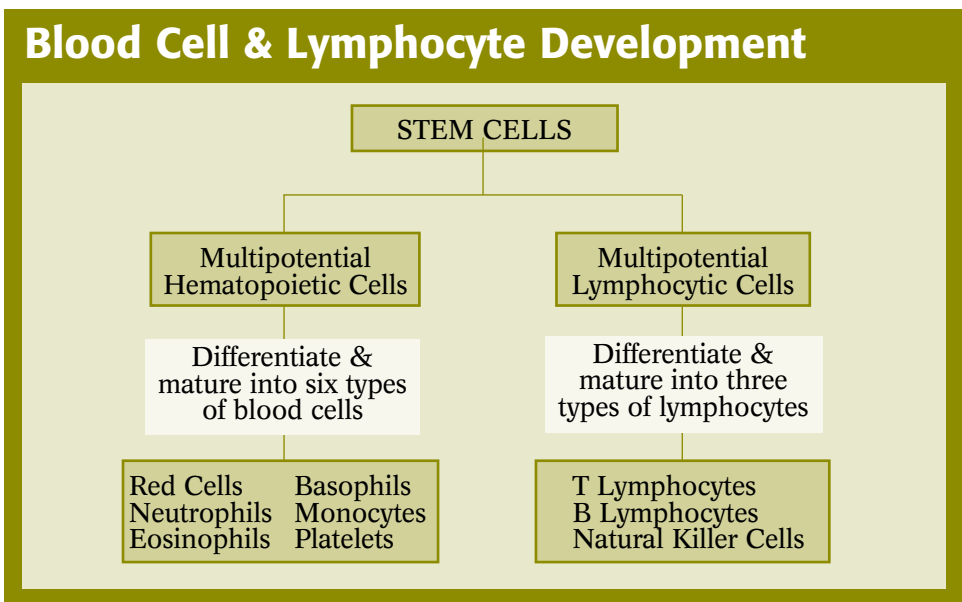


Figure 1. This simplified diagram depicts the process in which stem cells develop into functional blood cells (hematopoiesis) and lymphatic cells.

When the cells are formed and functional, 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 then transplanted into a recipient (if enough stem cells can be 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. (To learn more about stem cell transplantation, see The Leukemia & Lymphoma Society’s [LLS] free booklet *Blood and Marrow Stem Cell Transplantation* and the fact sheet *Cord Blood Stem Cell Transplantation*.)

Myelodysplastic Syndromes

MDS originates from mutations in a normal stem cell (a multipotential hematopoietic cell) in the marrow (see Figure 1, page 4). With MDS, blood cell production in the marrow is usually increased and the marrow becomes filled with more than the normal number of developing blood cells. The blood is usually deficient in cells because the developing cells in the marrow die as they approach maturity, before they would normally be released into the blood. This leads to reduction in the number of circulating red cells (anemia), neutrophils (neutropenia) and platelets (thrombocytopenia).

However, marrow cell disturbances in MDS patients can range from mild to very severe. In certain patients, the MDS cells remain functional and enter the blood. The red cells that are made carry oxygen, the white cells (neutrophils and monocytes) can ingest and kill bacteria, and the platelets can plug up injury to blood vessels. In more severe cases of MDS, blood cell formation is more disordered and abnormal blast cells accumulate in marrow and blood. These cells do not mature into functional cells. In particular, the cells are much less capable than their normal counterparts of maturing into red cells, neutrophils and platelets.

Normally, immature cells known as “blasts” make up less than five percent of all cells in the marrow. In MDS patients, blasts often comprise more than five percent of the cells. The number of blast cells—from cases with lower proportions of blast cells to cases with higher proportions of blast cells—is one of the principal determinants of disease severity. A patient with more than 20 percent blasts in the marrow is diagnosed with acute myelogenous (or myeloid) leukemia (AML).

MDS may be chronic or indolent (nonprogressive or progressing very slowly) and evident primarily as mild to moderate anemia. Or, MDS may be characterized by severe decreases in

- Red cells, white cells and platelets
- Blood cells and the presence of leukemic blast cells in the marrow and blood.

MDS can progress such that the abnormal blast cells take over the marrow and the disease “evolves” into AML. (For more information about AML, see the free LLS booklet *Acute Myelogenous Leukemia*.)

MDS has been known as “smoldering leukemia,” “preleukemia” or “oligoleukemia.” These terms may be misleading by implying that MDS is only problematic and potentially fatal after it has evolved to AML. Many patients ask whether MDS is “cancer.” MDS is a diagnosis of cancer. Cancer means that a mutation of a normal cell leads to the development of cells that no longer behave normally. However, the effect of a disease on a patient’s life is more important than the term used to describe the disease. It is important to know that the course of MDS can be slower and interfere less with quality of life than the course of diseases not considered “cancer,” such as congestive heart failure, emphysema or Parkinson disease.

Incidence

About 10,268 cases of MDS were diagnosed in the United States between 2001 and 2004 (source: Surveillance, Epidemiology, and End Results [SEER] Program, 2001-2004, National Cancer Institute, 2007). However, some researchers estimate that the numbers may actually be much higher.

Myelodysplastic Syndromes (MDS) Age-specific Incidence Rates (1975-2004)

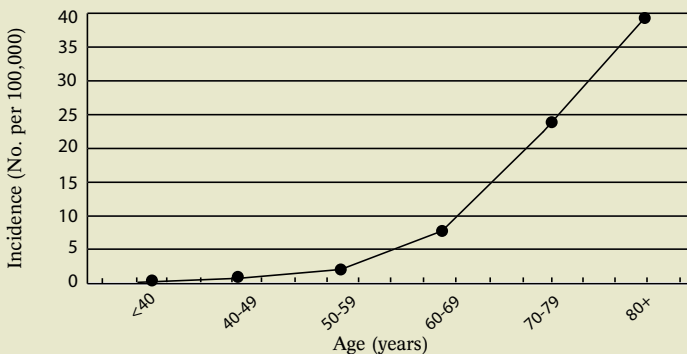


Figure 2. The horizontal axis represents the age of patients from under 40 years old and then in 10-year age increments. The vertical axis shows the frequency of new cases of MDS from 1975 to 2004, per 100,000 people by age-group. Source: Surveillance, Epidemiology and End Results (SEER) Cancer Statistics Review 1975-2004, National Cancer Institute, 2007.

The incidence of MDS increases with age, with the majority of patients being older than 60 years (see Figure 2, page 6). Men are affected slightly more often than women. MDS is much less common in children, in whom the disease is often associated with abnormal cells that have an acquired loss of chromosome 7.

Causes and Risk Factors

MDS may be “primary” (also called “de novo”) or “secondary” (cases that arise following treatment with chemotherapy and radiotherapy for other cancers, such as lymphoma, myeloma or breast cancer). Repeated exposure to the chemical benzene—which damages the DNA of normal stem cells—is another predisposing factor in MDS development. Benzene in cigarette smoke is now the most common known cause of exposure to this toxin. Benzene is also found in certain industrial settings. However, the stringent regulation of its use has diminished benzene exposure in the workplace.

Only a small proportion of people exposed to chemotherapy, radiation therapy and/or benzene develop MDS. A leading theory about why MDS develops in some people but not others is that the former have inherited genes that limit their ability to detoxify the causative agents. The vast majority of patients with MDS have primary MDS, which usually has no clear-cut triggering event.

Signs and Symptoms

Most often patients seek medical attention because of symptoms including fatigue and shortness of breath during physical activity, which result from a decreased number of red cells (called “anemia”). Some patients have no symptoms, and a diagnosis of MDS is made as a result of a routine physical examination accompanied by a blood test called a “complete blood count” (CBC).

Diagnosis

An MDS 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. A CBC confirms the presence of anemia and, for some patients, low numbers of neutrophils and platelets. The red cells are examined to find out if the anemia is due to MDS or to other causes, such as deficiencies of iron, folate, or vitamin B₁₂, other types of cancer, or conditions that lead to accelerated destruction (hemolysis) of red cells. If tests do not confirm one of these other causes of anemia, a sample of bone marrow is obtained by bone marrow aspiration and biopsy and then examined.

A diagnosis of MDS requires at least one of the following to be present in the marrow:

1. Blasts comprising more than five percent of the marrow cells
2. Cytogenetic abnormalities. "Cytogenetic" refers to chromosomes. MDS cells often have cytogenetic (chromosomal) abnormalities (damage to DNA). Abnormalities are also described as "simple" (fewer than three chromosomes affected) or "complex" (three or more chromosomes affected). The most common cytogenetic abnormalities seen in MDS involve
 - (a) A loss (deletion) of the long arm (q) of one of the two chromosome 5's (5q-), or of one of the two chromosome 7's (7q-), or of one of the two chromosome 20's (20q-)
 - (b) A complete loss of one of the two chromosome 5's (-5), or chromosome 7's (-7)
 - (c) Trisomy 8 (an extra copy of chromosome 8, so that there are three copies instead of two).
3. Obvious changes to the structure or form of the marrow (dysplasia).

Fluorescent in situ hybridization, often referred to as FISH, is a method that is used 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.

The presence of only mild dysplasia, in the absence of more than five percent blasts or a cytogenetic abnormality, may be insufficient to diagnose MDS. In such cases, it is important to have the patient's marrow slides examined by a hematopathologist, and in some cases a second hematopathologist, and to make sure that other causes of anemia or of low platelet or neutrophil counts are not present.

MDS Classification and the International Prognostic Scoring System

The International Prognostic Scoring System (IPSS), summarized in Table 1 on page 10 and Table 2 on page 11, is used by a large number of physicians who treat MDS patients. The IPSS, introduced in 1997, was devised in order to translate a patient's degree of disease severity from broad descriptions into an objective standard. The IPSS assigns patient-risk to one of four categories—low, intermediate-1, intermediate-2, or high. The IPSS categories of low and intermediate-1 are sometimes combined into a lower-risk group; the categories of intermediate-2 and high are sometimes combined into a higher-risk group. A patient's IPSS score is integrated with the physician's observations of the patient because the IPSS alone is not a precise predictor of risk. Current research is attempting to further identify patient-risk factors.

Historically, MDS has been classified into different subtypes that were based on the appearance of the patient's marrow and the results of the blood cell counts. In 1982 the French-American-British (FAB) Work Group, devised a classification of MDS. The FAB classification of MDS consists of five subtypes:

1. Refractory anemia (RA)
2. Refractory anemia with ringed sideroblasts (RARS)
3. Refractory anemia with excess blasts (RAEB)
4. Refractory anemia with excess blasts in transformation (RAEB-T)
5. Chronic myelomonocytic leukemia (CMML).

In 1999 the World Health Organization (WHO) modified the FAB classification of MDS. The WHO-modified classification differs from the FAB in a number of ways. The WHO classification

- Incorporates molecular and cytogenetic data
- Defines patients with more than 20 percent blasts in the marrow as having AML
- Has a new category of “myelodysplastic syndromes/myeloproliferative disorders” (MDS/MPD), which includes juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML)
- Adds the subtypes 5q- syndrome, refractory cytopenia with multilineage dysplasia (RCMD) and unclassifiable MDS (MDS-u)
- Considers RAEB-T to be a leukemia rather than a subtype of MDS.

Some physicians use the FAB classification or the WHO classification of MDS in combination with the IPSS to estimate risk and survival. The IPSS and other classifications are also useful in interpreting the results of cooperative clinical trials involving patients at different treatment centers.

Note that MDS subtype definitions are included in the *Glossary*, which begins on page 24.

Table 1. International Prognostic Scoring System (IPSS)

Factor	Notes	Value	IPSS Score
Blasts		5% or less	0
		5% to 10%	0.5
		11% to 20%	1.5
		21% to 30%	2.0
Cytogenetics	Normal; -Y only; 5q- only; or 20q- only	=Good	0
	Complex; 3 or more abnormalities or abnormal chromosome 7	=Intermediate	0.5
	All other abnormalities	=Poor	1.0
Cytopenias	Hemoglobin <10 g/dL; absolute neutrophil count (ANC) <1,500/ μ L; platelet count <100,000/ μ L: Each count as a value of 1.	0/1	0
		2/3	0.5

Table 1. The IPSS is used to assess risk and evaluate treatment for MDS patients. Patients with blast counts greater than 20 percent are diagnosed with acute myelogenous leukemia (AML).

The method for determining the IPSS risk category is to convert each of the following three patient disease factors into a numerical score:

- The percentage of marrow leukemic blast cells
- The severity of chromosomal changes in the marrow cells
- The presence of one or more cytopenias; for example, anemia, anemia with low white cell counts, or anemia with low white cell counts and low platelet counts.

The patient’s combined score for all of the factors places him or her in one of the four risk categories.

Table 2. IPSS Risk Categories

IPSS Score*		Risk Category
0	=	IPSS low
0.5-1.0	=	IPSS intermediate-1
1.5-2.0	=	IPSS intermediate-2
≥ 2.5	=	IPSS high

*See Table 1, page 10.

Table 2. The individual scores for marrow blast percentage, cytogenetics (chromosomal changes) and cytopenias (low red cell count, low neutrophil count and/or low platelet count) are combined to give the total IPSS score. See examples of total scores, below.

Examples of total scores:

- A patient with five percent or less marrow blasts, no cytogenetic abnormalities, a hemoglobin of less than 10 grams per deciliter (<10 g/dL) (anemia) with normal platelet counts and normal neutrophil counts would have a score of 0. This patient would be considered IPSS low risk.
- A patient with five to 10 percent blasts and a deletion of chromosome 7, and with both anemia and a platelet count of less than 50,000 per microliter (µL) would have an IPSS score of 1.5. This patient would be considered IPSS intermediate-2.

Treatment

It is important for MDS patients to be treated by a physician, usually a hematologist-oncologist, who specializes in treating blood disorders including MDS. The goals of therapy for MDS vary based on patient factors, including whether the patient is in a low- or high-risk category and how old the patient is. In general, the goal of treatment for patients with lower-risk MDS is to manage the disease by reducing their transfusion needs, decreasing the risk of infection and increasing the number of good quality years of life.

At the present time, the only potentially curative therapy for MDS—high-dose chemotherapy with allogeneic stem cell transplantation (allotransplantation)—is only a practical option for younger patients with higher-risk MDS who have a matched donor and whose life expectancy without successful treatment warrants the risk of undergoing the transplant procedure. There are many patients with MDS whose prognosis is considered good enough that it would not make sense to undergo allotransplantation. For patients with lower-risk MDS, the benefits of this treatment generally do not outweigh the risks involved.

There are a number of general approaches to treatment, which may be used alone or in combination (see Table 3, page 14). These include

- Observation with periodic blood counts (watch and wait)
- Transfusions and iron chelation therapy
- Administration of erythropoietin (EPO) and other growth factors
- Therapy with antithymocyte globulin (ATG)
- Drug therapy with azacitidine, decitabine, or lenalidomide
- Chemotherapy of the type used to treat acute myelogenous leukemia (AML)
- Chemotherapy of the type used to treat AML, followed by allogeneic stem cell transplantation.

Observation (Watch and Wait). Observation with periodic blood counts (watch and wait). “Watch and wait” is generally recommended for a patient with an IPSS low or intermediate-1 risk, a hemoglobin level greater than 10 g/dL and platelet counts greater than 50,000 per microliter (μL) to 100,000 per microliter (μL) without need for transfusion. Such patients may be able to maintain their usual activity levels without treatment.

It is important to have a physician who is familiar with MDS 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, periodic surveillance is important since there is a risk of progression to a more severe disturbance in blood cell formation, which in the extreme is AML.

Transfusions. In some patients, treatment to improve blood cell counts may lead to alleviation of symptoms. Periodic red cell or platelet transfusions may be needed. The decision to give red cell transfusions is based on a combination of factors, including the patient’s hemoglobin level, symptoms—for example, feelings of fatigue or shortness of breath—and any other health complications, such as heart disease.

Red cells contain iron and patients who have ongoing transfusion needs (ranging from less than 2 units to 4 or more units of blood a month) may be at risk for “iron overload”—a condition which can potentially damage the heart and liver. A blood test called a “serum ferritin level,” which measures the body’s store of iron, is used to monitor the patient. There are two medications called “iron chelators” that are FDA-approved to remove excess iron in the body because of transfusion-dependent anemias. Deferasirox (Exjade®) is an oral medication (a tablet to dissolve in liquid), taken once a day. Deferoxamine mesylate (Desferal®; DFO) is administered as a slow subcutaneous or intramuscular infusion for 8 to 12 hours per day, five to seven days per week.

Platelet transfusions are typically required once a patient’s platelet count is less than 10,000/ μ L. However, the major indication for platelet transfusion is unusual bleeding or bruising.

LLS offers a free booklet, *Blood Transfusion*, which provides comprehensive information on transfusion of red cells, white cells, platelets and other blood components for patients with MDS and other blood cancers.

Erythropoietin (EPO) and Other Growth Factors. In some patients with troublesome decreases in blood cell counts, agents that can stimulate blood cell production, called “growth factors,” may be useful.

EPO is a hormone produced in the kidneys that stimulates red cell production. Red blood cell growth factors, called “erythropoietin-stimulating agents (ESAs),” such as Procrit® and Aranesp® are synthetic forms of EPO and are given by injection under the skin (subcutaneous injection). Aranesp® is a longer-acting form of EPO than Procrit®.

ESAs can be used to treat the 10 to 20 percent of MDS patients who have anemia that is associated with low EPO levels. For this subgroup, usually IPSS low or intermediate-1 risk patients, treatment with EPO will decrease transfusion needs and possibly improve survival.

Most patients with MDS do not have low EPO levels, and administration of ESAs is not useful in treating their anemia. However, all patients with MDS should have their EPO levels checked. Some MDS patients with low EPO levels may not benefit from ESAs alone, but ESAs combined with granulocyte-colony stimulating factor (G-CSF)—a hormone that increases white cell production—may increase their hemoglobin levels.

Used alone, G-CSF, or another white cell growth factor called granulocyte macrophage-colony stimulating factor (GM-CSF), have no role in treating MDS. However, G-CSF or GM-CSF may be used to treat patients with low neutrophil counts who develop infections. Prompt attention to infection or unexplained fever is 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.

AMG 531 is a new drug being investigated in clinical trials for MDS patients with low platelet counts.

Table 3. Some Types of Therapy for Myelodysplastic Syndromes

Growth factors

(Examples: epoetin alfa, darbepoetin alfa and granulocyte-colony stimulating factor [G-CSF])

Drug therapy

(Examples: azacitidine, decitabine, lenalidomide)

AML-type chemotherapy

(Examples: cytarabine and daunorubicin, cytarabine, idarubicin, mitoxantrone and thalidomide)

Stem cell transplantation

(Examples: allogeneic, reduced-intensity allogeneic)

Antithymocyte globulin (ATG; Thymoglobulin®; Atgam®). Some MDS patients have disease characterized by lymphocytes that destroy precursors of normal red cells, neutrophils and platelets. ATG is an immune globulin that is obtained from rabbits or horses and is given intravenously, destroys these lymphocytes and improves blood counts in some MDS patients. Fever and chills are common immediately after ATG administration. It is possible to identify patients with better (usually patients with low or intermediate-1 IPSS risk) or worse chances of responding to ATG. Patients should talk to their physicians about whether they might benefit from treatment with ATG.

Drug Therapy. Three single-drug approaches, azacitidine, decitabine and lenalidomide, have been approved by the U.S. Food and Drug Administration (FDA) for treatment of MDS.

- Azacitidine (Vidaza®). This drug, known as a “hypomethylating” or “demethylating” agent, is FDA-approved for the treatment of both low- and high-risk patients. It appears to help the patient’s bone marrow begin to function more normally. It also kills the unhealthy cells in bone marrow that have been reproducing abnormally. Azacitidine is given by injection under the skin, usually for seven consecutive days, every four weeks.

On average, about 40 percent of patients respond to azacitidine. Treatment with this drug has been shown to lead to improved quality of life, based on comparing groups of patients in two multicenter, randomized studies. One patient-group received observation, with transfusions as needed. The other group received observation, with transfusions as needed, and azacitidine. In both studies, the addition of azacitidine reduced transfusion needs. Azacitidine does cause side effects, such as nausea, vomiting and diarrhea, and also temporarily reduces blood counts. However, blood counts usually return to, or surpass, pretreatment levels prior to the next weekly series of injections.

Oral azacitidine is being studied in phase 1 clinical trials to determine the most appropriate dose and its effectiveness.

- **Decitabine** (Dacogen®). This drug, another hypomethylating/demethylating agent that is FDA-approved for low- and high-risk patients, is given intravenously. Decitabine has also been studied in a randomized trial comparing treatment with observation and transfusions alone to observation and transfusions with decitabine. Like azacitidine, decitabine reduced transfusion needs and improved blood counts in 30 to 40 percent of patients. However, further study is needed to determine the most effective doses of decitabine. Other randomized trials are currently investigating this.

- **Lenalidomide** (Revlimid®). 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 of the long arm of chromosome 5 (del 5q), either with or without additional cytogenetic abnormalities, and is the preferred therapy for such patients. A 5q deletion may be involved in 20 to 30 percent of all MDS cases. Lenalidomide is an immunomodulatory drug that is a nonneurotoxic and nonsedating derivative of thalidomide.

It produces and maintains red cell transfusion independence in the majority of low-risk del 5q patients for about two years. Lenalidomide also reduces red cell transfusion requirements in low-risk patients without del 5q, but not as effectively as in patients with del 5q. Further study is needed to understand lenalidomide's effect on life expectancy and its benefits for patients with IPSS intermediate-2- or high-risk MDS, with or without del 5q.

Further studies are needed to determine which of these drugs (azacitidine, decitabine or lenalidomide) are best for patients with low-risk MDS without del 5q who have high EPO levels and hence are unlikely to respond to ESAs.

Chemotherapy. Patients in the intermediate-2 and high-risk IPSS categories may require treatment with the same type of chemotherapy that is used to treat acute myelogenous leukemia (AML). Planning this form of treatment also takes into account the patient's age and any coexisting medical conditions.

These are some of the drugs that may be used:

- Cytarabine (cytosine arabinoside, ara-C; Cytosar-U®)
- Idarubicin (Idamycin®)
- Daunorubicin (Cerubidine®)
- Mitoxantrone (Novantrone®).

The drugs may be given alone or in combinations of two or three different agents (combination chemotherapy). In some cases, low-dose protocols are used.

Initially, the application of chemotherapy will make the patient's blood cell counts worse. This means that the physician has to assess whether intensive chemotherapy is warranted, considering both the severity of the cell disturbances and the potential for the patient to respond to the chemotherapy with a remission.

Chemotherapy has rarely cured patients with the common types of MDS (those patients with abnormalities of chromosomes 5 and/or 7). Newer drugs, such as clofarabine (Clolar[®]), are being explored in clinical trials to treat both MDS and AML patients. (See *Research and Clinical Trials*, beginning on page 18.)

More information about these drugs is in the free LLS booklet *Understanding Drug Therapy and Managing Side Effects*.

Allogeneic Stem Cell Transplantation (Allotransplantation). Allotransplantation is a high-risk procedure, and the decision to perform a transplant depends on several factors. For patients who are under age 55, and are in either the IPSS intermediate-2 or high-risk categories and have an HLA-matched stem cell donor (sibling or unrelated), intensive radiation and/or chemotherapy, followed by allogeneic stem cell transplantation, is the therapy with the best known potential to cure their disease.

About 40 to 50 percent of patients who have an allotransplant will be cured of their MDS. Outcomes of transplants with stem cells from matched-unrelated donors compare well to outcomes of transplants with matched-related donors. Some patients relapse after transplantation, although if relapse occurs, it is usually within the first few years.

Allotransplantation has been largely limited to patients with high-risk MDS because of the significant allotransplant-associated mortality rates (10 to 30 percent). Nonmyeloablative allogeneic transplantation (reduced-intensity stem cell transplantation) clinical trials are under way to determine the usefulness of this approach in older patients. Reduced-intensity transplants are almost as effective in eliminating MDS as standard (fully myeloablative) allogeneic transplants and may have lower mortality rates than those associated with standard allogeneic transplantation. As a result, transplantation may be an option for patients above age 60 to 70, who comprise the great majority of MDS patients. The effectiveness of reduced-intensity transplantation is due to the “graft versus MDS effect” of the donor’s lymphocytes rather than to high doses of chemotherapy. (See *Research and Clinical Trials* on page 18.)

See the free LLS publications *Blood and Marrow Stem Cell Transplantation* and *Cord Blood Stem Cell Transplantation* for comprehensive information about stem cell transplantation.

Treatment Outcomes. Better supportive care, treatment with newer agents (lenalidomide, azacitidine and decitabine), progress in stem cell transplantation and studies of new drugs in clinical trials are all contributing to improved outcomes and quality of life for MDS patients. Nevertheless, the prognosis of MDS varies widely, and all patients are advised to discuss survival information with their physicians. Patients may want to keep in mind that existing survival statistics may underestimate survival to a small degree since these data do not incorporate outcomes of current treatment options. High-risk patients are encouraged to talk to their physicians about whether it might be of benefit to participate in a clinical trial.

Research and Clinical Trials

LLS is funding research that could lead to treatments to repair damaged DNA in MDS patients.

Clinical Trials. The goal of clinical trials for MDS and other blood cancers is to improve treatment and quality of life and to increase survival. Clinical trials are carefully planned and monitored research studies, conducted by doctors. A treatment that is proven safe and effective in a clinical trial is often approved by the FDA for use as a standard treatment if it is more effective or has fewer side effects than the current standard treatment.

Before a clinical trial begins, a new therapy is developed and extensively tested in a laboratory. Then it is thoroughly tested in several species of animals. If the preclinical trials show that the therapy is safe and effective, a multiphase clinical trial will then be conducted in humans. Each phase has a specific purpose, and when a phase is successfully completed, the trial can move to the next phase. In a phase 1 trial a relatively small number of patients—for whom there is no known effective therapy—is studied to assess dosage, patient tolerance and acute toxic effects for a new treatment. In a phase 2 trial, more patients are studied and more information is gathered on dosage, effects and toxicity. In a phase 3 trial, the treatment is compared in larger numbers of patients, who are randomized to receive the existing best treatment or the new (study) treatment. Phase 4 studies are conducted for new drugs or treatments that already have FDA approval; the goals are to identify additional uses for the drug or treatment, gather additional safety and effectiveness information from a larger group of patients, and establish effectiveness in specific subgroups of patients, for example, in patients older than 65 years.

Patients' participation in clinical trials is needed to improve standard therapies so that all MDS patients can one day be cured of their disease. Clinical trials are under way to study treatments for newly diagnosed patients—or patients with relapsed or refractory MDS—with low-risk, intermediate-risk or high-risk MDS.

Clinical trials can involve new drugs, new combinations of drugs or approved drugs that are being studied to treat patients in new ways—for example, new drug dosages or schedules of administration (see Table 4).

Drug Therapy. There are several clinical trials to study treatment with combinations of FDA-approved drugs, such as azacitidine or decitabine, and AML-type chemotherapy. The idea of combining agents is that since they each work in different ways to kill cancer cells, using them together may kill more MDS cells—or be as effective as standard MDS therapies, but with less-toxic side effects. Azacitidine is also being studied as maintenance therapy for MDS patients who achieve a complete or partial remission after intensive chemotherapy. The purpose of the study is to see if the duration of patient response is improved with azacitidine maintenance.

Table 4. Some Drugs Being Studied in Clinical Trials to Treat Myelodysplastic Syndromes

Arsenic trioxide (Trisenox®)
Clofarabine (Clolar®)
Lonafarnib (Sarasar®)
Tipifarnib (Zarnestra®)
Valproic acid (Depakene®)
Vorinostat (Zolinza®)

Table 4. Some of the drugs being studied to treat MDS are already approved to treat other diseases or conditions. For example, valproic acid is approved to treat certain seizure disorders and vorinostat is approved to treat a form of lymphoma.

Some of the clinical trials are for all MDS-risk types; others are for either lower-risk or higher-risk MDS. Patients should speak to their physicians about the benefits of treatment in a specific clinical trial. Eligibility for the trials may depend on the patient's age, risk type and previous treatment for MDS.

Examples of the drug combinations under study are

- Arsenic trioxide (Trisenox[®])—a drug used principally to treat acute promyelocytic leukemia—in combination with azacitidine (Vidaza[®]) or with tipifarnib (Zarnestra[®]), a farnesyl transferase inhibitor (FTI), and gemtuzumab ozogamicin (Mylotarg[®]), a monoclonal antibody. Mylotarg[®] is approved to treat CD33-positive acute myelogenous leukemia (AML) patients 60 years or older who are in first relapse and who are not considered candidates for other cytotoxic chemotherapy.
- Clofarabine (Clolar[®])—a drug approved to treat childhood relapsed or refractory acute lymphocytic leukemia (ALL)—in combination with AML-type chemotherapy.
- Lonafarnib (Sarasar[®]), a farnesyl transferase inhibitor (FTI). It is being studied in MDS patients who receive between one and eight platelet transfusions every four weeks.
- Valproic acid (Depakene[®]), a histone deacetylase inhibitor (HDAC inhibitor), in combination with decitabine (Dacogen[®]).
- Vorinostat (Zolinza[®]), a histone deacetylase inhibitor (HDAC inhibitor), in combination with azacitidine (Vidaza[®]).

Vaccine Therapy. Clinical trials are under way to determine if an MDS vaccine could be effective in treating patients aged 18 years and older with lower-risk MDS. The vaccine is made from protein-building blocks (called “peptides”) that may help the body marshal an effective immune response to MDS cells.

Vaccine therapy and donor lymphocyte infusions are also being studied to treat MDS (and other blood cancer) patients with progressive or relapsed disease following allogeneic stem cell transplantation.

Reduced-Intensity Stem Cell Transplantation. Studies of nonmyeloablative allogeneic stem cell transplantation are under way 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 Effects

Living with a serious disease is a challenge—for the patient, family members and others who care. No one response to a diagnosis of MDS is either universal or unexpected. However, many patients feel emotional relief once they can reestablish a sense of control in their lives. It may take a while; however, most people with MDS are able to cope with a diagnosis that at first may seem hard to accept. With information and support, many people shift their focus to the therapy process and the prospect of recovery.

Initially, patients may want to focus on learning about the type of MDS they have and its treatment. Patients and caregivers are advised to discuss the disease and its treatment, to ask questions and to convey fears or concerns to the patient's physicians, nurses, social workers and other members of the healthcare team—they are available to spend time with the patient, answer questions, lend emotional support and provide referrals to other useful resources.

Patients may want to have friends, family members or caregivers help them obtain and process medical and support information. The presence of another individual may help ease the patient's stress. This person can also help the patient ask questions and record and retain information. While it is not always possible to have this type of support, patients can reach out in other ways—for example, local or Internet support groups can provide a forum for discussion. Often, patients with MDS become acquainted with one another, and these friendships provide support. Over time, some patients form supportive relationships with members of their healthcare team.

Treatment for MDS may mean changes in daily life, at least for a time. For some patients, hospitalizations will be necessary. For most patients, disease and treatment side effects and concerns about survival, finances, work or family life may cause the person to question his or her self-worth or identity. These issues may affect relationships, including intimate relationships. Recognition that these feelings are normal and knowing that many side effects are temporary may be reassuring. Open, honest communication regarding fears and concerns can be very helpful.

Finances. Cancer treatment can be financially difficult for many families due to loss of income and the high cost of many medications and procedures. LLS offers financial reimbursement for some medications, transportation and procedures for

those in need through the *Patient Financial Aid Program*. Through the *Co-Pay Assistance Program* LLS offers patients assistance with private health insurance premiums, private insurance co-pay obligations, Medicare Part B, Medicare Plan D, Medicare Supplementary Health Insurance and Medicare Advantage premium or co-pay obligations. Prescription drugs covered under this program include those supplied to the patient by a pharmacy or administered in an office or hospital by a healthcare provider. Public or private prescription drug coverage is required to qualify for this program.

Depression. It is important to seek medical advice if a patient’s mood does not improve over time—for example, if a patient is feeling depressed every day for a two-week period. Depression is an illness that should be treated even when a person is undergoing treatment for MDS. Treatment for depression has proven benefits for people living with cancer. There are many sources of help available to patients and caregivers. Aspects of care such as making treatment choices, finding the time and money for medical care and communicating with family members and friends can be stressful. Contact LLS or ask the healthcare team for guidance and referrals to other sources of help such as support groups, counseling services and community programs. The National Institute of Mental Health (NIMH) has several publications about depression that may be helpful. For more information go to www.nimh.nih.gov and enter “depression” in the search box at the top of the Web page, or call the NIMH at (866) 615-6464.

Children’s Concerns. MDS is uncommon in children. Each family living with a childhood MDS diagnosis is thrown into an unfamiliar world. The child, parents and siblings need support. Remember that help is available. Don’t hesitate to ask for assistance for your child, yourself or other family members, even if you are already working with a psychologist, social worker or child life specialist. Many families will benefit from extra support.

A child with MDS may be hospitalized. For some children this is the first time they have stayed away from home. Providing age-appropriate information to your child about the illness and treatment will help him or her build trust in both you and the treatment team and feel comfortable talking about fears and concerns. For practical guidance on how to support your child and other family members, deal with your own concerns, share the news with extended family and friends and make the transition to life after treatment ends, see the free LLS booklet *Coping With Childhood Leukemia and Lymphoma*.

We Can Help. LLS also offers financial assistance and support programs through its national office and local chapters to help ease the economic and emotional pressure that comes with a cancer diagnosis. Visit www.LLS.org or contact our Information Resource Center at (800) 955-4572 to locate a chapter in your area, order free publications or speak directly to an Information Specialist.

For more information, see the free LLS booklets and fact sheets.

Acute Myelogenous Leukemia; 2007.

Acute Myelogenous Leukemia: A Guide for Patients and Caregivers; 2007.

Blood and Marrow Stem Cell Transplantation; 2007.

Chronic Myelomonocytic Leukemias (fact sheet); 2002.

Coping With Childhood Leukemia and Lymphoma; 2007.

Each New Day: Ideas for Coping with Leukemia, Lymphoma or Myeloma; 2006.

Essential or Primary Thrombocythemia (fact sheet); 2007.

Fertility Facts; 2007

Food and Nutrition Facts; 2007

Idiopathic Myelofibrosis (fact sheet); 2007.

Learning & Living with Cancer: Advocating for your child's educational needs; 2006.

Polycythemia Vera (fact sheet); 2007.

Sexuality and Intimacy (fact sheet); 2008

Understanding Clinical Trials for Blood Cancers; 2006.

Understanding Drug Therapy and Managing Side Effects; 2007.

For children:

Pictures of My Journey: Activities for kids with cancer; 2007.

The Stem Cell Transplant Coloring Book; 2007.

Glossary

Absolute Neutrophil Count (ANC)

The number of neutrophils (a type of white cell) that a person has to fight infection. It is calculated by multiplying the total number of white blood cells by the percentage of neutrophils.

Acquired Sideroblastic Anemia See Refractory Anemia with Ringed Sideroblasts.

Acute Myelogenous Leukemia (AML)

A progressive cancer that starts with the malignant transformation of an immature cell in the marrow. The affected cell is usually 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. Synonyms for AML include “acute nonlymphocytic leukemia,” “acute myeloid leukemia,” and “acute myelocytic leukemia.” (See the free LLS booklet *Acute Myelogenous Leukemia*.)

Allogeneic Stem Cell Transplantation

A treatment that uses donor stem cells to restore a patient’s marrow and blood cells. First, the patient is given “conditioning therapy” (high-dose chemotherapy or high-dose chemotherapy with total body radiation) to treat the disease and to “turn off” the patient’s immune system so that the donor stem cells will not be rejected. A type of transplant called a “nonmyeloablative” transplant (also called a “reduced-intensity” transplant) is under study. For a reduced intensity transplant, lower doses of conditioning therapy are used, which may be safer, especially for older patients. (For more information, see the free LLS 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.

Antigen

A foreign substance, usually a protein, that stimulates an immune response when it is ingested or inhaled or comes into contact with the skin or mucous membranes. Examples of antigens are bacteria, viruses or allergens. Antigens stimulate plasma cells to produce antibodies.

Apheresis

The process of removing components of a donor's blood and returning the unneeded parts to the donor. The process, also called "hemapheresis," uses continuous circulation of blood from a donor through an apparatus and then back to the donor. This process makes it possible to remove desired elements from large volumes of blood. Platelets, red cells, white cells and 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.

Aplastic Anemia

A condition in which the bone marrow is unable to produce blood cells. Some persons with aplastic anemia have cells in their marrow with abnormal features that are similar to MDS cells and not typical of aplastic anemia.

Autologous Stem Cell Infusion (Autotransplantation)

A technique, often referred to as "autologous stem cell transplantation" or "autotransplantation," involving 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, such as acute myelogenous leukemia, when in remission or when the marrow and blood are not overtly abnormal (for example, in lymphoma). Technically, this procedure is not transplantation, which implies taking tissue from one person (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. (For more information, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.)

Basophil

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

Blast Cells

The earliest marrow cells identified by the light microscope. Blasts represent about one percent of normally developing marrow cells. They are largely myeloblasts, which are cells that will develop into neutrophils. In normal lymph nodes, blasts are lymphoblasts; that is, cells that are part of lymphocyte development. In the acute leukemias, blast cells similar in appearance to normal blast cells accumulate in large numbers, constituting up to 20 percent of all marrow cells. In myelodysplastic syndromes and acute myelogenous leukemia, myeloblasts accumulate, and in acute lymphocytic leukemia, lymphoblasts accumulate. Normal myeloblasts give rise to granulocytes (neutrophils, eosinophils and basophils). With myelodysplastic syndromes, abnormal myeloblasts displace or otherwise interfere with the production of normal red cells, white cells and platelets in the marrow. 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

Any of the three main types of cells in the blood: red cells, which carry oxygen; white cells, which principally prevent or combat infections; and platelets, which 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 it serves. 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 live for a week or two, and white cells live for a few days. The marrow must replace over 500 billion cells 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 cell count” or “CBC” is often used to refer to this test.

Bone Marrow

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

Bone Marrow Aspiration

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

Bone Marrow Biopsy

A test to examine marrow cells to detect cell abnormalities. This test differs from a bone marrow aspiration in that a small amount of bone filled with marrow is removed, usually from the hip bone. After medication is given to numb the area, a special biopsy needle is used to remove a core of bone containing marrow. The marrow is examined under a microscope to determine if abnormal cells are present. Bone marrow aspiration and biopsy may be done in the doctor's office or in a hospital. The two tests are almost always done together. Both tests are also done after treatment to determine the proportion of blood cancer cells that have been killed by therapy.

Bone Marrow Transplantation See Allogeneic Stem Cell Transplantation; Autologous Stem Cell Infusion.

Central Line See Indwelling Catheter.

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, gastrointestinal tract, skin and hair follicles are most sensitive to these chemicals, injury to these organs causes the common side effects of chemotherapy; for example, mouth sores and hair loss.

Chromosome

Any of the 46 structures in the nucleus of all cells in the human body (except the red blood cells) that contain a strand of DNA. This strand is made up principally of genes, which are specific stretches of the DNA. “Genome” is the term for an organism’s complete set of DNA. It is estimated that the human genome has about 30,000 genes. The genes on the X and Y chromosomes are the determinants of our gender: two X chromosomes in females and an X and a Y chromosome in males. Each chromosome has a long arm (called “q”) and a short arm (called “p”). The number or shape of chromosomes may be altered in myelodysplastic syndromes as a result of chromosome breakage, deletions or other abnormalities.

Clonal

The designation for a population of cells derived from a single transformed parent cell. Virtually all cancers are derived from a single cell with an injury to its DNA (mutation) and thus are monoclonal. Leukemia, lymphoma, myeloma and myelodysplastic syndromes are examples of clonal cancers; that is, cancers derived from a single abnormal cell.

Clonal Anemia, Clonal Pancytopenia

Terms that may be used instead of “acquired” or “refractory” anemia. The terms “acquired” and “refractory” do not indicate the malignant (cancerous) nature of these disorders. A clonal disorder is a 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 prevent the rejection of the graft. Second, it markedly decreases the marrow cells, which may be important to open up the special niches where the transplanted stem cells must lodge to engraft. Third, if the patient is being transplanted for a malignancy, this intensive therapy greatly decreases the numbers of any remaining tumor cells.

Cytogenetic Analysis

The process of analyzing the number and size of the chromosomes of cells. In addition to detecting chromosome alterations, in some cases it is possible to identify the actual genes that have been affected. These findings are very helpful in diagnosing specific types of leukemia and lymphoma, in determining treatment approaches and in following the response to treatment. The individual who prepares and examines the chromosomes and interprets the results is called a “cytogeneticist.”

Cytokines

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) and granulocyte macrophage-colony stimulating factor (GM-CSF) are two such cytokines. They stimulate the production of neutrophils and shorten 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

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

Deletion

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

DNA

The abbreviation for deoxyribonucleic acid, the material inside the nucleus of cells that carries 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. Genes tell the cell how to make the proteins that enable it to carry out its functions. DNA can become highly abnormal in cancer cells.

Donor Lymphocyte Infusion (DLI)

A therapy that involves giving lymphocytes from the original stem cell donor to a patient who has had an allogeneic bone marrow transplant with a relapse of disease. DLI may induce an immune reaction against the patient's cancer cells. This therapy has been most effective in patients with chronic myelogenous leukemia who relapse after transplantation but is being studied to treat patients with myelodysplastic syndromes and other blood cancers.

Eosinophil

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

Erythrocytes See Red Cells.

Erythropoietin (EPO)

A hormone required for the normal production of red blood 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 (Procrit® or Epogen®) 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 myelodysplastic syndromes. These drugs stimulate red cell production by the same mechanism as EPO; that is, by interacting with the EPO receptor on red cell progenitors.

Farnesyl Transferase Inhibitor (FTI)

A drug that has the potential to kill cancer cells by inhibiting or reversing the effect of farnesyl transferase, an enzyme needed to activate oncogenes (cancer-causing genes). FTIs, including tipifarnib (Zarnestra®) and lonafarnib (Sarasar®), are being studied to treat myelodysplastic syndromes and other blood cancers.

FISH See Fluorescent In Situ Hybridization.

5q- syndrome, 5q minus syndrome

A disorder of myeloid marrow cells that causes refractory (treatment-resistant) anemia associated with a deletion of the long arm (q arm) of chromosome 5 (del 5q). It affects about 20 to 30 percent of patients with myelodysplastic syndromes.

Fluorescent In Situ Hybridization (FISH)

A technique that can be used to see if cytogenetic abnormalities characteristic of MDS, or other blood cancers, are in the nucleus of the patient's cancer cells. FISH uses DNA-binding agents that are specific for the pieces of DNA (parts of chromosomes) of interest. FISH can be helpful in assessing treatment needs and monitoring treatment effectiveness by providing a sensitive test to see abnormal cells, such as cells with deletions of 5q.

G-CSF See Granulocyte-Colony Stimulating Factor.

GM-CSF See Granulocyte Macrophage-Colony Stimulating Factor.

Graft Versus Tumor (GVT) Effect

The potential immune reaction of transplanted T lymphocytes to recognize and attack the malignant cells of the recipient. This effect was noted when: 1) disease recurrence after transplant was seen to be more likely if the donor and recipient were identical twins than if they were nonidentical siblings; 2) the more prominent the graft versus host disease the less likely was disease recurrence; and 3) the removal of donor T lymphocytes decreased the incidence of graft versus host disease but also resulted in a higher frequency of disease relapse. Each of these observations could be explained best by an immune attack by donor lymphocytes against recipient tumor cells that collaborated with the intensive conditioning treatment to keep the disease in check. This effect seems to be most active in myeloid leukemia, although it may also occur in patients with other blood cancers.

Granulocyte

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

Granulocyte-Colony Stimulating Factor (G-CSF)

A cytokine that stimulates the production of granulocytes (neutrophils, basophils and eosinophils) types of white blood cells—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.” (See Cytokines.)

Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF)

A cytokine that stimulates growth of granulocytes (neutrophils, basophils and eosinophils) and macrophages—types of white blood cells—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.” (See Cytokines.)

Growth Factors See Cytokines; Granulocyte-Colony Stimulating Factor; Granulocyte Macrophage-Colony Stimulating Factor.

Hemapheresis See Apheresis.

Hematocrit

The proportion of the blood occupied by the red cells. Normal values are 40 to 54 percent in males and 35 to 47 percent in females. If the hematocrit is below normal, the condition is called “anemia”. If the hematocrit is above normal, the condition is called “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.

Hematology

The study of blood diseases, including leukemia, lymphoma, myeloma, myelodysplastic syndromes and myeloproliferative disorders.

Hematopathologist

A pathologist who specializes in the diagnosis of blood cell diseases and who performs the specialized laboratory tests often required to make a conclusive diagnosis.

Hematopoiesis

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 such as 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 that most blood cells live for short periods and must be continually replaced. Red cells die in four months, platelets in 10 days and most neutrophils in two or three days. About 500 billion blood cells are made each day.

Hemoglobin

The iron-containing pigment in red cells that carries oxygen to the tissue cells. A reduction in the number of red cells decreases the amount of hemoglobin in the blood. A decreased blood hemoglobin concentration is called “anemia.” A low 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 16 grams per deciliter (g/dL). Healthy women have on average about 10 percent less hemoglobin in their blood compared to men.

Histone Deacetylase Inhibitor (HDAC Inhibitor)

A substance that causes a chemical change that stops cancer cells from dividing. HDAC inhibitors—for example, valproic acid (Depakene®) and vorinostat (Zolinza®)—are being studied in the treatment of myelodysplastic syndromes and other blood cancers. HDAC inhibitors appear to have a greater effect on cancer cells than on normal cells. As a result they may cause less toxicity than other chemotherapeutic agents.

HLA

The abbreviation for human leukocyte-associated 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 (for example, in identical twins) or very similar (for example, in HLA-matched siblings), the transplant (donated stem cells) is more likely to survive (engraft) in the recipient. In addition, the recipient’s body cells are less likely to be attacked by the donated immune cells (a result called “graft versus host disease”).

Immunophenotyping

A method that uses the reaction of antibodies with cell antigens to determine a specific type of cell in a sample of blood cells, marrow cells or lymph node cells. The antibodies react with specific antigens on the cell. A tag is attached to an antibody so that it can be detected. The tag can be identified by the laboratory detector used for the test. As cells carrying their array of antigens are tagged with specific antibodies, they can be identified; for example, myeloid blast cells can be distinguished from lymphoid blast cells. The antigen on a cell is referred to as a “cluster of differentiation” or “CD,” with an associated number. For example, CD33 may be present on myeloid blasts.

Indwelling Catheter

Several types of catheters (the Groshong®, 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 be used for outpatient chemotherapy or blood product administration. Another type of long-term catheter incorporates an implanted port. The port is surgically inserted under the skin's surface on the upper chest wall. After the site heals, no dressings are needed and no special home care is required. When medicines are needed, a physician, physician assistant or nurse inserts a needle through the skin to access the port. The patient can choose to have a numbing cream applied locally at the injection site before the port is used. Blood can be drawn and blood products can be received through this device.

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). (See Fluorescent In Situ Hybridization.)

Leukocytes See White Cells.

Leukopenia

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

Macrophage See Monocyte.

Marrow See Bone Marrow.

MDS-u See Unclassified MDS.

Monoclonal See Clonal.

Monoclonal Antibodies

Antibodies made by cells belonging to a single clone. These highly specific antibodies can be produced in the laboratory. They are very important reagents for identifying and classifying disease by the immunophenotyping of cells. They also have clinical applications for targeted delivery of drugs to cancer cells and can be used to purify cells used for stem cell transplants.

Monocyte (Macrophage)

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

MPD See Myeloproliferative Disorders.

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 that specific tissue cell into a tumor. Most cancers start after a somatic mutation. In leukemia, lymphoma or myeloma, a primitive marrow or lymph node cell undergoes somatic mutation(s) that lead(s) to the formation of a tumor. 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.

Myelodysplasia See Refractory Anemia; Refractory Anemia with Ringed Sideroblasts.

Myelodysplastic/Myeloproliferative Disorders (MDS/MPD) See Myeloproliferative Disorders.

Myeloproliferative Disorders (MPDs)

A group of diseases in which specific types of blood cells are overproduced by the body. Examples of myeloproliferative disorders are essential thrombocythemia, polycythemia vera and idiopathic myelofibrosis. Some persons with MPDs have abnormal-looking cells in their bone marrow that are similar to cells of myelodysplastic syndromes and are not typical of MPDs. The World Health Organization (WHO) MDS classification includes the category “myelodysplastic/myeloproliferative disorders” (also referred to as “MDS/MPD overlap”) that includes juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML).

Neutropenia

A decrease below normal in the number of blood 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 infection. Often, it is not present in sufficient numbers in patients with myelodysplastic syndromes or after chemotherapy, thus increasing the patient’s susceptibility to infection. A neutrophil may be called a “poly” (for “polymorphonuclear”) or “seg” (for “segmented nucleus”).

Nonmyeloablative Allogeneic Stem Cell Transplantation See Reduced-Intensity Stem Cell Transplantation.

Oligoblastic Myelogenous Leukemia

A more accurate term for describing 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 does not always prove to be true.

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.

Pancytopenia

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

Pathologist

A physician who identifies disease by studying tissues under a microscope. (See Hematopathologist).

Phagocytes

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

Platelets

Small cell fragments (about one-tenth the volume of red cells) that stick to the site of blood vessel injury, aggregate 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 may be needed to support MDS patients. Platelet transfusions are rarely given unless the patient’s platelet count is below 10,000 per microliter of blood. The platelets can be pooled from several unrelated donors and given as pooled, random-donor platelets. The platelets from about 6 one-unit blood donors are required to significantly raise the platelet count in a recipient. Sufficient platelets can be obtained from one donor by a procedure known as “apheresis.” This technique skims the platelets from 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 various 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. (See HLA.)

RA See Refractory Anemia.

RAEB See Oligoblastic Myelogenous Leukemia.

RAEB-T See Refractory Anemia with Excess Blasts in Transformation.

RARS See Refractory Anemia with Ringed Sideroblasts.

RCMD See Refractory Cytopenia with Multilineage Dysplasia.

Red Cells

Blood cells (erythrocytes) that carry hemoglobin, which binds oxygen and carries it to the tissues of the body. The red cells make up about 40 to 45 percent of the volume of the blood in healthy individuals.

Reduced-Intensity Stem Cell Transplantation

Stem cell transplantation that involves preconditioning with administration of chemotherapy plus or minus radiation that is not given in the full doses administered in standard allogeneic stem cell transplantation. This term is sometimes used as a synonym for “nonmyeloablative” or “mini” transplantation. The theory being tested with a reduced-intensity transplant is that by undergoing less-toxic procedures prior to the transplant, the body is better able to withstand the transplant. However, full donor engraftment still takes place, and the desired graft versus tumor effect still occurs.

Refractory Anemia (RA)

In some classification systems, the name for a subtype of myelodysplastic syndromes. Refractory anemia is a clonal myeloid disorder that primarily affects red cell production in the marrow. RA is often associated with mild to moderate decreases in white cells and platelets. The disorder is also referred to as “myelodysplasia.”

Refractory Anemia with Excess Blasts (RAEB) See Oligoblastic Myelogenous Leukemia.

Refractory Anemia with Excess Blasts in Transformation (RAEB-T)

A subtype of myelodysplastic syndromes in the French-American-British (FAB) classification in which the bone marrow blast count ranges from 20 to 30 percent.

Refractory Anemia with Ringed Sideroblasts (RARS)

In some classification systems, the name for a subtype of myelodysplastic syndromes characterized by refractory anemia (RA) with an abnormal accumulation of iron granules around the nucleus. These cells are called “ringed sideroblasts.” 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. RA and RARS are often associated with mild to moderate decreases in the numbers of white cells and platelets. This disorder is also referred to as “myelodysplasia” or “acquired sideroblastic anemia.”

Refractory Cytopenia with Multilineage Dysplasia (RCMD)

A subtype of MDS in the World Health Organization (WHO) classification that includes patients with less than 10 percent abnormal cells in two or three blood cell types with blast levels less than five percent in marrow and less than one percent in blood, and less than 15 percent ringed sideroblasts in the marrow. The presence of more than 15 percent ringed sideroblasts is referred to as RCMD-RS.

Refractory Disease

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

Relapse

A return of 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” and “partial” are used to modify the term “remission.” Complete remission means that all evidence of the disease is gone. Partial remission means that the disease is markedly improved by treatment, but residual evidence of the disease is present.

Resistance to Treatment

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 condition in which a proportion of malignant cells resist the damaging effects of a drug or drugs. Cells have several ways to develop drug resistance.

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, the extent of exposure and its duration are important considerations in determining if risk is increased.

Stem Cells

The multipotential 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. (See Hematopoiesis.) Using special techniques, the stem cells in blood can be collected, preserved by freezing and, later, thawed and used for stem cell therapy.

Stem Cell Transplantation See Allogeneic Stem Cell Transplantation; Autologous Stem Cell Infusion.

Thrombocytopenia

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

Unclassified MDS (MDS-u)

A subtype of MDS in the World Health Organization (WHO) classification that includes patients who do not have refractory anemia or other MDS subtypes, but have either neutropenia or thrombocytopenia with unusual features, for example, marrow fibrosis. The number of blasts in the blood and bone marrow is not increased.

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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Visit the “Select Reading List” at www.LLS.org to see suggested books on a wide range of topics.

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