

# Understanding Myelodysplastic Syndromes: A Patient Handbook

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## WHAT IS MDS?

Myelodysplastic Syndromes (MDS) are a group of diverse bone marrow disorders in which the bone marrow does not produce enough healthy blood cells. In research circles, MDS is referred to as a bone marrow failure disorder. MDS is primarily a disease of the elderly (most patients are older than age 70), but MDS can affect younger patients as well.

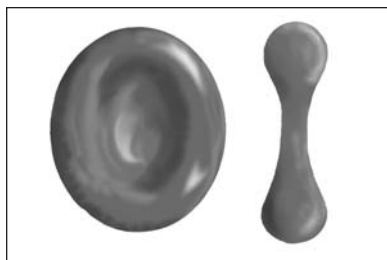
To help you better understand MDS, it might be helpful to first consider some basics about bone marrow and blood. The bone marrow functions as a factory that manufactures three kinds of blood cells: red blood cells, white blood cells, and platelets. Healthy bone marrow produces immature blood cells—called stem cells, progenitor cells, or blasts—that normally develop into mature, fully functional red blood cells, white blood cells, and platelets. In MDS, these stem cells may not mature and/or they may have a shortened life span. In fact, these cells may die in the bone marrow before being released into the circulation, resulting in a disproportionate number of these blasts in the bone marrow and fewer than normal mature blood cells in the circulation. Low blood cell counts, referred to as cytopenias, are a hallmark feature of MDS and are responsible for some of the symptoms that MDS patients experience—namely, infection, anemia, spontaneous bleeding, or easy bruising. Anemia, neutropenia, and thrombocytopenia are the major types of blood cell cytopenias, and are discussed below.

In addition to the disproportionate numbers of blasts in the marrow and blood cells in the circulation, the mature blood cells circulating in the blood may not function properly because of dysplasia. The formal definition of dysplasia is the abnormal shape and appearance, or morphology, of a cell. The prefix *myelo-* is from the Greek and it means marrow; so *myelodysplasia* refers to the abnormal shape and appearance—or morphology—of the mature blood cells found in the bone marrow.

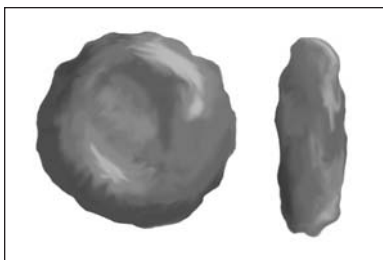
Failure of the bone marrow to produce mature healthy cells is a gradual process, and therefore MDS is not necessarily a terminal disease. However, some patients do succumb to the direct effects of the disease: reduced blood cell and/or platelet counts may be accompanied by the loss of the body's ability to fight infections and control bleeding. In addition, for roughly 30% of the patients diagnosed with MDS, this type of bone marrow failure syndrome will progress to acute myeloid leukemia (AML).

### EFFECT ON RED BLOOD CELLS

The bone marrow produces red blood cells, which when mature, carry oxygen to the body's tissues via a blood protein called hemoglobin. The percentage of red blood cells in the total blood volume is called the hematocrit. In healthy women, the hematocrit is 36% to 46%, whereas in healthy men, the hematocrit is 40% to 52%. When the hematocrit falls below the normal range, there is an insufficient number of red blood cells and consequently too little hemoglobin to effectively supply oxygen to all tissues of the body. This condition of below-normal numbers of red blood cells, low hemoglobin levels, and low oxygen is called anemia, which can be relatively mild (hematocrit of 30% to 35%), moderate (25% to 30%), or severe (less than 25%). Anemia can also result from the inefficient transport of oxygen by dysplastic (mature but misshapen) red blood cells.



*Healthy, mature red blood cells*



*Abnormal or "dysplastic" red blood cells*

## EFFECT ON WHITE BLOOD CELLS

In addition to red blood cells, the bone marrow also produces white blood cells, which are key cells of the body's immune system and prevent and fight infection. The bone marrow normally makes between 4,000 and 10,000 white blood cells per microliter of blood; in African-Americans the range is lower, between 3,200 and 9,000 white blood cells per microliter. There are several types of white cells, including neutrophils (alternatively known as granulocytes), which primarily fight bacterial infections and lymphocytes, which primarily fight viral infections.

Most MDS patients develop neutropenia, or a low white blood cell count. MDS patients with neutropenia usually have too few neutrophils. Neutropenia elevates the risk of contracting bacterial infections such as pneumonia and urinary tract infections.

Some MDS patients who have not yet developed neutropenia still suffer recurrent infections. Although the count is normal, white blood cells are not able to function as well as those in a healthy person. Researchers are exploring the role of an "immunological defect" in the development of MDS.

## EFFECT ON PLATELETS

Platelets, which are critical to blood coagulation and the formation of clots to stop bleeding, are also produced by the bone marrow. Healthy bone marrow normally manufactures between 150,000 and 450,000 platelets per microliter of blood; however, most patients with MDS have a low platelet count, or thrombocytopenia. Patients with thrombocytopenia may suffer from bruising or small cuts may take longer than normal to stop bleeding. Severe thrombocytopenia, which is uncommon, is defined as a platelet count below 20,000, and is associated with numerous bleeding problems.

## WHAT CAUSES MDS?

With a few exceptions, the exact causes of MDS are unknown. Some evidence suggests that certain people are born with a tendency to develop MDS. This tendency can be thought of as a switch that is triggered by an external factor. If the external factor cannot be identified, then the disease is referred to as "primary MDS".

Radiation and chemotherapy for cancer are among the known triggers for the development of MDS. Patients who take chemotherapy drugs or who receive radiation therapy for potentially curable cancers, such as Hodgkin's disease

and non-Hodgkin's lymphoma, are at risk of developing MDS for up to 10 years following treatment. MDS that develops after use of cancer chemotherapy is called "secondary MDS" and is usually associated with multiple chromosome abnormalities in cells in the bone marrow. This type of MDS often develops rapidly into AML.

Exposure to certain environmental or industrial chemicals, such as benzene, can also trigger MDS. Unfortunately, it is not clear which other chemicals may predispose individuals to MDS, although certain occupations have been labeled "at risk" for the development of MDS or AML (e.g., painters, coal miners, embalmers). There are no known food or agricultural products that cause MDS. While alcohol consumed on a daily basis may lower red blood cell and platelet counts, alcohol does not cause MDS. As for tobacco, insufficient data are available to determine if smoking increases the risk of developing MDS. However, it is known that the risk of developing AML is 1.6 times greater for smokers than for non-smokers.

Patients and their families often worry that MDS might be contagious. No evidence exists to suggest that a virus causes MDS; thus, MDS cannot be transmitted to loved ones. Because they are not at increased risk of developing MDS, family members do not need to have routine blood counts. In fact, it is a very rare occasion when family members, including siblings, are diagnosed with MDS.

## WHAT ARE THE SYMPTOMS OF MDS?

Many patients in the early stages of MDS experience no symptoms at all. A routine blood test may reveal a reduced red cell count, or low hematocrit, sometimes along with reduced white cell and/or platelet counts. On occasion, the white cell and platelet counts may be low while the hematocrit remains normal. In the early stages of this disease, the counts are usually not so reduced that they produce symptoms. However, some patients, particularly those with blood cell counts well below normal, experience definite symptoms. These symptoms, described below, depend on which blood cell type is involved as well as the level to which the cell count drops.

### LOW RED CELL COUNT (ANEMIA)

Anemic patients generally experience fatigue and report that they are tired much of the time and have no energy. Anemia varies in its severity. In mild anemia, patients may feel well or just slightly fatigued. In moderate anemia, almost all patients experience some fatigue, which may be accompanied by heart palpitations, shortness of breath, and pale skin. In severe anemia, almost all patients appear pale and suffer severe fatigue and shortness of breath. Because severe anemia reduces blood flow to the heart, older patients may be more likely to experience cardiovascular symptoms, including chest pain.

### LOW WHITE CELL COUNT (NEUTROPENIA)

A reduced white cell count lowers the body's resistance to bacterial infection. Patients with neutropenia may be susceptible to skin infections, sinus infections (symptoms include nasal congestion), lung infections (symptoms include cough, shortness of breath), or urinary tract infections (symptoms include painful and frequent urination). Fever may accompany these infections.

## LOW PLATELET COUNT (THROMBOCYTOPENIA)

Patients with thrombocytopenia have an increased tendency to bruise and bleed even after minor bumps and scrapes. Bruises can be dramatic, some as large as the palm of the hand. Nosebleeds are common and patients often experience bleeding of the gums, particularly after dental work. Before having dental work, consultation with your hematologist, who may prescribe the prophylactic use of antibiotics, is recommended since infection and bleeding pose a risk for most MDS patients.

## WHAT TESTS ARE USED TO DIAGNOSE MDS?

### BLOOD TESTS

The initial step in making a diagnosis of MDS is to have a blood test using a blood sample drawn from the arm. The blood sample is then evaluated for cell counts (red blood cells, white blood cells and their subtypes, and platelets), shape and size of the red and white blood cells, and the level of erythropoietin (EPO) in the serum. EPO, a protein produced by the kidneys in response to low oxygen in body tissues, stimulates the production of red blood cells in the bone marrow.

If the blood test indicates that the red blood cells are misshapen (dysplastic), the patient could possibly have a Vitamin B<sub>12</sub> or folate deficiency. As happens in MDS and AML, this vitamin deficiency results in dysplasia (misshapening) of the red blood cells, making these cells less efficient in transporting oxygen to the body's tissues. To rule out Vitamin B<sub>12</sub> and folate deficiencies as the cause of anemia, levels of these vitamins in the blood are also measured.

### BONE MARROW EXAMINATION

If the blood test indicates that a patient is anemic, with or without a low white cell and/or platelet count, the bone marrow may be examined. Bone marrow examination includes a bone marrow aspirate, in which a sample of the liquid marrow is taken, and a bone marrow biopsy (a sample of the boney portion of the bone marrow). The procedure is discussed in more detail later.

The bone marrow is examined for (1) the percentages of blasts and dysplastic blood cells, (2) iron content of the red blood cells, and (3) chromosome abnormalities, such as missing or extra chromosomes in a blood cell. Any abnormalities are described in a report of hematologic findings, and chromosome abnormalities (missing or deleted chromosomes or changed or extra chromosomes or parts of chromosomes) are identified in a report of cytogenetic findings. The physician or pathologist uses a microscope to examine the cells in the bone marrow aspirate and biopsy samples. Periodic bone marrow exams are often used to determine if MDS has progressed over time.



*Cross-section of the hip*

### ***Procedure Used in the Bone Marrow Examination***

A bone marrow examination can be performed in the physician's office and it usually takes about twenty minutes. A mild sedative or narcotic may be given to the patient. The patient reclines on the examining table, on either their stomach or the side, whichever position is most comfortable. The physician feels for the bony protrusion on the right or left back side of the hip, known as the posterior iliac crest. This site, not the spine, is the location used for the bone marrow examination of MDS patients. The physician swabs the skin with iodine and places a sterile towel and drape over the area to reduce the risk of bacterial infection.

A needle, smaller than one used to draw blood from the arm, is slowly inserted under the skin to inject a local anesthetic. The patient may feel a slight burning sensation, but the area is quickly numbed. Next, a longer, slightly larger needle is used to inject anesthetic into the bone itself. It is common for patients to experience a twinge of pain when the second needle is inserted. Once the needle makes contact with the bone, the patient should only feel a slight pressure, as though a thumb were pressing against the skin.

The physician will wait about five minutes or until the bone covering, or periosteum, is well anesthetized. If the patient continues to have sensation, the physician will wait a little longer or additional anesthetic can be injected into the area. Afterwards, the physician proceeds with a third, larger needle, which is inserted into the bone marrow. (Since there are no nerve endings in the marrow, this stage should be painless.) While asking the patient to take several slow, deep breaths, the physician attaches a syringe to the end of the needle and then quickly pulls out, or aspirates, the liquid portion of the marrow (about a tablespoon in total). Typically the patient experiences a shock-like sensation during this part of the procedure but just for a fraction of a second. Often a second aspiration is done to obtain additional marrow for evaluation of both the percentage of blast cells and for cytogenetic testing.

Finally, a fourth, larger bore needle is inserted to obtain a narrow (several millimeter diameter) core of the bone for biopsy. As the needle is being inserted into the bone, the patient should feel nothing more than dull pressure. When the physician loosens the bone and removes it, the patient experiences a jerking sensation. The bone marrow extraction is over, and the patient is readied for departure. For safety reasons, the patient should have a friend, family member, or care taker travel home with them; the patient should not drive.

### ***Risks of a Bone Marrow Examination***

Some risks accompany a bone marrow examination, including infection, bruising and bleeding, and discomfort. Anytime a needle is inserted through the skin, there is a possibility of infection. However, infection is highly unlikely to occur if antiseptic conditions are maintained throughout the procedure.

After the examination, some patients develop a sizable bruise or a swelling of blood (hematoma) under the skin, particularly those whose platelet count is low. If the platelet count is below 50,000 platelets per microliter, the physician will apply at least five minutes of pressure over the needle site.



Discomfort is a common fear of patients who face a bone marrow examination. This fear can be reduced if you know that a bone marrow examination is similar to a tooth being pulled. In each case, the bone is “pricked.” If this is properly done, there should be little pain other than the twinge of the needle going under the skin.

Some patients express a preference for general anesthesia. General anesthesia has its own risks; however, and is not necessary for a bone marrow examination. If the patient remains concerned that a local anesthetic will not be adequate, additional medication may be requested.

## HOW SEVERE IS MY MDS?

Because the disease course of MDS can vary widely from patient to patient, classification systems for grouping MDS “subtypes” have been developed. The most recently proposed classification system, called The World Health Organization (WHO) classification system, recognizes six distinct MDS subtypes based on large, worldwide patient data sets and better understanding of the disease processes involved in MDS.

The previous, widely used system is the French-American-British (FAB) classification system. Some hematologists still use this system.

Another system that describes the aggressiveness of MDS and the prognosis for the patient is the International Prognostic Scoring System (IPSS).

### FRENCH-AMERICAN-BRITISH (FAB) CLASSIFICATION

The FAB Classification was developed in the early 1980s by a group of physicians with expertise in diagnosing MDS from France, the United States, and Great Britain. The central criterion for classification in the FAB system was the percentage of blast cells in the bone marrow, with less than 2% blasts considered normal for healthy bone marrow. The FAB classification recognized five MDS subtypes:

- refractory anemia (RA)
- refractory anemia with ringed sideroblasts (RARS)
- refractory anemia with excess blasts (RAEB)
- refractory anemia with excess blasts in transformation (RAEB-t)
- chronic myelomonocytic leukemia (CMML)

### WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION

The WHO classification system for MDS in adult patients has preserved some of the elements of the FAB classification system and has expanded the categories of MDS subtypes. The major features of the six MDS subtypes recognized by the WHO classification system are highlighted in the table.

It is not yet clear whether the WHO classification system will be adopted globally by physicians. Only time will tell. One obstacle to immediate acceptance of the WHO system is related to clinical trials of experimental drugs begun before the introduction of the WHO system: some trials still in progress categorized patients enrolled in the trial using the FAB system and therefore the study findings must be analyzed in the context of the originally assigned FAB subtypes.

Noteworthy changes between the WHO and FAB classification systems include:

- combining of RA and RARS subtypes into a single subtype
- separation of RAEB into two subtypes
- elimination of CMML as its own subtype
- addition of 5q- syndrome as its own subtype
- elimination of refractory anemia with excess blasts in transformation (RAEB-t), which is now considered to be included under AML
- creation of a category called unclassified MDS

<b>WHO Classification of MDS</b>	
<b>MDS Subtype</b>	<b>Description</b>
<b>RA/RARS</b>	Minimal dysplasia in one blood cell type (red blood cells or erythrocytes) and <5% blasts in the bone marrow
<b>RCMD</b>	Dysplasia (>10%) in 2 or 3 blood cell types and <5% blasts and <15% ringed sideroblasts in the bone marrow. (Presence of >15% ringed sideroblasts is referred to as RCMD-RS.)
<b>RAEB</b>	
<b>RAEB 1</b>	Presence of 5% to 9% bone marrow blasts
<b>RAEB 2</b>	Presence of 10% to 19% bone marrow blasts
<b>MDS/MPD</b>	Dysplasia but features also commonly seen in myeloproliferative disorders; includes CMML
<b>5q- syndrome</b>	Patients with no chromosome abnormality other than a deletion in the long arm of chromosome #5
<b>Unclassified MDS</b>	Includes patients with single blood cell type cytopenia other than anemia (i.e., neutropenia or thrombocytopenia) and unusual features (e.g., marrow fibrosis)

**RA/RARS: Refractory anemia (RA) and with refractory anemia ringed sideroblasts (RARS).** Patients in this category have anemia that is not responsive, that is, it is refractory, to iron or vitamin therapy. The anemia may be accompanied by mild to moderate thrombocytopenia and neutropenia. Sideroblasts are red blood cells containing granules of iron; ringed sideroblasts are abnormal.

Refractory anemia with or without ringed sideroblasts (RA/RARS) is considered the most benign subtype in the WHO classification system. Under this system, MDS patients with the RARS/RA subtype have disease that is restricted to the red blood cell or erythrocyte. The dysplasia observed in this MDS subtype is minimal.

**Refractory cytopenia with multilineage dysplasia (RCMD).** Patients with refractory cytopenias (persistently low counts of any of the blood cells types; e.g., refractory neutropenia or refractory thrombocytopenia) and minimal dysplasia in more than one blood cell types and less than 5% blasts or less than 15% ringed sideroblasts are included in this category. When a patient with RCMD has greater than 15% ringed sideroblasts, the diagnosis is RCMD-RS.

**Refractory anemia with excess blasts (RAEB).** This category is divided into two subcategories, distinguished by the number of blasts in the bone marrow. Patients with RAEB-1 are those with 5 to 9% blasts and patients with RAEB-2 have 10 to 19% blasts.

**Myelodysplastic/myeloproliferative disease (MDS/MPD).** Patients with MDS/MPD include those with chronic myelomonocytic leukemia (CMML), which was its own category in the FAB classification system.

**5q- (5q minus) syndrome.** The 5q- syndrome, now recognized as a true MDS subtype, was originally described more than 30 years ago. The syndrome's name refers to chromosome number 5, specifically to a chromosomal abnormality (a deletion) in the long arm (q) of chromosome #5. A deletion within the long arm of chromosome #5 can be the only chromosomal abnormality in MDS patients diagnosed with 5q- syndrome. MDS patients who have deletions within the long arm of chromosome #5 and other chromosomal abnormalities do not have 5q- syndrome.

Patients with 5q- syndrome have refractory anemia that requires supportive care. The syndrome usually occurs in middle-aged women, generally 65 years of age, with mild to moderate degrees of anemia and low white blood cell counts (leukopenia), and often with normal to elevated platelet counts. The 5q- syndrome is associated with survival times longer than 5 years from the time of diagnosis.

**Unclassified MDS.** This unclassified MDS category will likely comprise no more than 1% or 2% of all MDS cases. The category was created to accommodate the few patients with single blood cell type cytopenias (e.g., thrombocytopenia or neutropenia) and unusual features (e.g., fibrosis in the bone marrow).

## **INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS)**

A system for grading the severity of MDS is the International Prognostic Scoring System (IPSS). Following a patient's evaluation (findings from physical examination and blood tests), the disease is "scored" in terms of the risk to the patient, that is, life expectancy and the chances of progression or transformation of the disease to AML. The IPSS Score is a function of the percentage of blasts appearing in the bone marrow, the cytogenetic findings (identification of chromosomal abnormalities) in bone marrow blood cells, and the blood cell counts and other blood test findings.

The IPSS Score is determined by adding the individual scores for the percentage of blasts and for the cytogenetic and blood test findings, and is used to assess the clinical outcome for the MDS patient. The IPSS Score indicates which of the following risk groups a patient falls into:

- **Low-Risk Group:** IPSS Score of 0.
- **Intermediate-1 Risk Group:** IPSS Score of 0.5 to 1.0.
- **Intermediate-2 Risk Group:** IPSS Score of 1.5 to 2.0.
- **High-Risk Group:** IPSS Score over 2.0.

### Determining the IPSS Score

**IPSS Score:** Total of individual score values for blasts, cytogenetic finding, and blood-test findings

<b>Blasts in Bone Marrow</b>	<b>Score Value</b>
5% or less	0.0
5–10%	0.5
11–20%	1.5
21–30%*	2.0
<b>Cytogenetic Finding<sup>†</sup></b>	
Good	0.0
Intermediate	0.5
Poor	1.0
<b>Blood-test Findings<sup>‡</sup></b>	
0 or 1 of the findings	0.0
2 or 3 of the findings	0.5

\* Patients whose marrow contains more than 30% blasts have acute myeloid leukemia (AML).

<sup>†</sup> “Good”: normal set of 23 pairs of chromosomes, or a set having only partial loss of the long arm of chromosomes #5 or #20, or loss of the Y chromosome. “Intermediate”: Other than “Good” or “Poor” “Poor”: Loss of one of the two #7 chromosomes (“monosomy 7”), addition of a third #8 chromosome (“trisomy 8”), or three or more total abnormalities.

<sup>‡</sup> Blood-test Findings defined as: Neutrophils <1,800 per microliter;

Hematocrit <36% of red blood cells in total body volume; Platelets <100,000 per microliter

The physician will review the data collected from the blood tests and bone marrow examination and then will apply the WHO or FAB classification system and IPSS to determine the severity of the disease and the patient’s prognosis. (Use the boxed “Table of Test Results and Disease Severity” to record your personal data.) The physician will recommend a treatment program based on the degree to which symptoms can be relieved, blood abnormalities reduced, and the risk of progression to AML minimized.

### Table of Test Results and Disease Severity

<b>Parameter (units)</b>	<b>Normal Result</b>	<b>My Result</b>
Hematocrit (% red cells in blood)	36–52%	_____
White cell count (cells/μl blood)	3,200–10,000	_____
Platelet count (platelets/μl blood)	150,000–450,000	_____
Serum erythropoietin level (IU/L)	10–20	_____
Blast frequency (% of bone marrow cells)	<2%	_____
<b>Cytogenetic findings*</b>		
(Good, Intermediate, Poor)	Good	_____
WHO classification	Not applicable	_____
FAB classification	Not applicable	_____
IPSS classification	Not applicable	_____
Vitamin B <sub>12</sub> and/or folate deficiencies (No, Yes)	No	_____

\*See footnotes to table “Determining the IPSS Score”

## HOW IS MDS TREATED?

Treatment of MDS depends on a patient's symptoms, disease stage, disease risk category, age, pre-existing conditions, and the availability of a suitable (preferably related) marrow donor for blood or marrow transplantation. Numerous therapies continue to be investigated for their ability to either eradicate or suppress the abnormal dysplastic blasts in the bone marrow or to stimulate maturation of healthy blasts.

Treatment strategies for MDS include the following, which may be used alone or in combination:

- supportive care (symptom management) via red blood cell transfusions or platelet transfusion, antibiotics, and other medications
- stimulation of healthy blasts in the bone marrow through administration of growth factors (e.g., EPO, GM-CSF)
- removal or killing ("ablation" or "myeloablation") of abnormal blasts using chemotherapy
- removal or killing ("ablation" or "myeloablation") of abnormal blasts with chemotherapy, followed by blood or marrow transplantation (BMT), in which healthy bone marrow tissue or blood cells from a donor are transfused into the patient

At this time, bone marrow transplantation (also called or hematopoietic stem cell transplantation) is the only curative treatment currently available for MDS. However, this does not mean that all MDS patients are eligible for BMT or that those who undergo blood or marrow transplantation will be completely cured.

### APPROVED TREATMENTS FOR MDS

At present, three drugs have been approved by the U.S. Food & Drug Administration (FDA) for the treatment of MDS, Vidaza™, Revlimid®, and Dacogen™. All three drugs are currently under review for authorized use as prescription medicines by the European drug regulatory agency (European Agency for the Evaluation of Medicinal Products, or EMEA).

#### *Vidaza™ (azacytidine)*

Vidaza was the first drug approved specifically to treat MDS. Vidaza may be appropriate for any MDS subtype. It is administered by subcutaneous (under the skin) injection. Several clinical trials showed that, compared with patients who did not receive Vidaza, MDS patients treated with one subcutaneous injection of Vidaza daily for 7 days every four weeks had durable hematologic improvements: increases in red blood cells and transfusion independence, increase in hemoglobin, increases in white blood cell or platelet numbers, and/or decrease in bone marrow blast percentage. All patients in the clinical trials received supportive care regardless of whether or not they received Vidaza. In some clinical trials, the time to onset of AML was significantly delayed in Vidaza-treated patients when compared with patients who did not receive Vidaza.

Vidaza works by preventing a cellular process (methylation) that silences the genes involved in controlling the development of cancer (e.g., the so-called tumor suppressor genes). Vidaza is categorized as a *DNA hypomethylating agent* because it inhibits DNA methylation of tumor suppressor genes that are commonly hypermethylated in some cancers, including MDS.

### **Revlimid® (lenalidomide)**

Revlimid is approved for anemic MDS patients with Low- or Intermediate-1 risk MDS, particularly those with 5q- syndrome that are transfusion-dependent. Revlimid is taken orally and is available in capsule form.

The findings from a key study in MDS patients with symptomatic anemia were published in the *New England Journal of Medicine* in 2005. After 16 weeks of receiving daily oral Revlimid therapy (for 21 days of a 28-day cycle), the majority of patients that were transfusion-dependent had a red blood cell response (63%), which led to transfusion independence. A red blood cell response was seen in 75% and 46% of patients classified as refractory anemia (RA) under the FAB system and refractory anemia with ringed sideroblasts (RARS), respectively. When the response data were analyzed by patients' cytogenetics, more than half (57%) with no chromosome abnormalities had a response, whereas 83% of those with 5q- syndrome had a response.

These data are exciting because transfusion independence positively impacts patients' quality of life (QOL). Most patients participating in the clinical trials experienced an initial but transient suppression of white blood cells and platelets, and some patients experienced side effects, such as itching, fatigue, diarrhea, and bone pain. Because Revlimid is an analog (chemical look-alike) of thalidomide, there is a potential for birth defects with its use. Because of this potential, the manufacturer of Revlimid, Celgene Corp., has set up a restricted distribution program called RevAssist<sup>SM</sup>. Only patients that enroll in and meet all of the conditions of the program are able to receive the drug.

Revlimid works by stimulating the immune system and is categorized as an immunomodulatory agent. However, other actions of lenalidomide— inhibiting new blood vessel growth (anti-angiogenesis) and stimulating cell death— may contribute to its effect.

### **Dacogen™ (decitabine)**

Dacogen is approved in the U.S. for use in all MDS subtypes and Intermediate-1, Intermediate-2, and High-risk IPSS groups. Positive findings from a major phase III clinical trial that compared Dacogen with supportive care in MDS patients were reported in the medical journal *Cancer* in April 2006. The trial evaluated Dacogen administered as an intravenous infusion over 3 hours at a dose of 15 milligrams per meter squared, every 8 hours for 3 days and repeated every 6 weeks. A total of 170 patients with intermediate to high-risk MDS participated in the trial; half of the patients received Dacogen and half received supportive care (e.g., red blood cell transfusions or antibiotics as needed). A significantly higher overall response rate was seen in patients receiving Dacogen with the responses lasting for about 10 months: 17% response for Dacogen-treated patients versus 0% for patients receiving standard of care. Patients who responded to Dacogen became or remained transfusion-independent.

Dacogen, (also called 5-deoxyazacytidine), is a DNA hypomethylating agent like Vidaza (azacytidine). This means that Dacogen works by preventing certain genes involved in controlling cancer from being silenced. In other words, Dacogen allows for the normal functioning of the tumor suppressor genes.

## EARLY STAGES OF MDS

### *Treatment of Anemia*

Many patients in the early stages of MDS experience anemia. In fact, about 80% of patients are anemic when they are initially diagnosed with MDS. Anemia is defined as a low, or below normal, red blood cell count. Anemia is characterized by a persistently low hematocrit or persistently low levels of hemoglobin.

Anemic patients typically have pale skin and experience fatigue and shortness of breath. They include MDS patients in the International Prognostic Scoring System's low-risk group or intermediate-1 risk group.

Although chronic anemia is seldom life threatening, it can drastically reduce a patient's quality of life. Therefore, most clinicians recommend growth factors (e.g., EPO or G-CSF) or blood transfusions for patients with symptoms of anemia.

**Erythropoietin or EPO (Aranesp®, Procrit®).** The “recombinant” form of this natural growth factor is used to treat symptoms associated with anemia; it stimulates the bone marrow to produce red blood cells. The treatment is most helpful for patients whose natural (blood serum) EPO level is below 500 International Units per liter and who do not need frequent transfusions. Some patients may derive additional benefit when EPO is combined with other growth factors that stimulate the bone marrow to produce white blood cells (see white cell growth factors, discussed later). The combination of EPO and the white blood cell growth factor called granulocyte colony-stimulating factor (G-CSF) appears to be most beneficial for anemic MDS patients in the International Prognostic Scoring System's low-risk or intermediate-1 risk group.

Recombinant EPO is available as two brand-name drugs, both of which increase red cell counts in treated patients. Procrit is typically given as 50–100 Units per kilogram three-times a week either intravenously or subcutaneously. Darbepoetin alfa (Aranesp®) is a related but different form of EPO. Aranesp has a “patient friendly” dosing schedule (300 micrograms once-weekly) and is most effective in patients with low-risk MDS that have low blood serum EPO levels (<500 Units per liter).

**Pyridoxine (Vitamin B<sub>6</sub>).** If the bone marrow stain shows deposits of iron in the red blood cells—an indication of sideroblastic anemia—then the patient might try taking 100 mg of vitamin B<sub>6</sub> twice a day. Insufficient levels of pyridoxine may be hereditary, may result from poor absorption of the vitamin from food, or may be a side-effect of certain drugs. Low vitamin B<sub>6</sub> levels will impede the body's use of amino acids, the building blocks of proteins that are essential to cell structure and function. Pyridoxine therapy can relieve sideroblastic anemia through increases in red cell counts for about 5% of MDS patients. As a caution, pyridoxine doses exceeding 100 mg twice daily can produce side effects such as tingling of the fingers.

**Red Blood Cell Transfusions.** Supportive therapy with regular or periodic red blood cell transfusions may be appropriate for anemic patients who experience fatigue or other symptoms that usually accompany anemia. Anemic patients who are candidates for regular or periodic blood transfusions include MDS patients in the International Prognostic Scoring System's low-risk or intermediate-1 risk group who are severely anemic, with a hematocrit

consistently less than 25% or hemoglobin levels less than 10 grams per deciliter of blood. Periodic transfusions are also appropriate for patients who are classified under the World Health Organization system or the French-American-British system as having sideroblastic anemia. Sideroblastic anemia is a condition characterized by red blood cells that are incapable of utilizing iron for the production of hemoglobin. Red blood cell transfusions may also be used as supportive care for other MDS subtypes.

The frequency of transfusions for anemic patients who experience fatigue and/or shortness of breath varies from patient to patient. Some patients may need red blood cell transfusions as often as once every 1 to 2 weeks while other patients may only need a transfusion once every 6 to 12 weeks. The frequency depends upon the patient's symptoms, hematocrit, or hemoglobin level in the blood. Typically, MDS patients who require periodic red cell transfusions receive two units every 2 to 6 weeks.

Supportive therapy with regular red cell transfusions can be extremely beneficial for patients with anemia. However, there are several concerns related to this type of therapy—red blood cells carry iron and, after repeated transfusions, a patient may end up with elevated levels of iron in the blood and other tissues. Iron overload is a potentially dangerous condition. Fortunately, it can be treated with iron-chelating drugs (*see Desferal and Exjade, discussed below*).

Other concerns related to red cell transfusions include the risk of retaining excess fluid, which may cause or exacerbate shortness of breath. Fortunately, the fluid build-up can usually be managed by intravenous administration of the diuretic furosemide (Lasix).

Transmission of viruses through blood transfusions is another concern. However, screening tests that can detect viruses in donated blood are used to keep the blood supply as safe as possible. The risk of transmittal of viruses, such as HIV, hepatitis B virus, hepatitis C, is extremely low.

Despite the concerns and risks, supportive therapy with regular red cell transfusions has been shown to improve the quality of life for patients with symptomatic anemia. A free support program called REACH (**R**esource, **E**ducation, & **A**ctions to **C**hange Your **H**ealth), developed by the manufacturer of the iron-chelating drug, Exjade (*see below*), is available for patients who receive regular blood transfusions for their anemia.

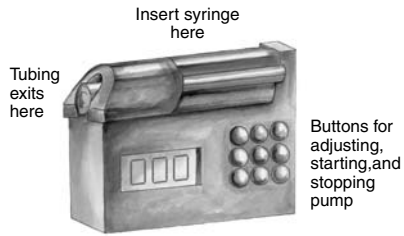
**Iron-Chelating Drugs.** Patients who are transfusion-dependent and require regular blood transfusions for their anemia may experience iron overload. Drugs that *chelate*, or bind to iron promote its removal from the body. At present, there are two FDA-approved prescription drugs for the treatment of transfusion-dependent iron overload: Desferal and Exjade. Another iron chelator, deferiprone, is licensed for use in Europe and other countries (but not the U.S.) for patients with iron overload who are unable to use Desferal because of intolerability or lack of effectiveness.



### **Desferal® (deferroxamine).**

Deferoxamine can significantly delay the toxic effects of iron build-up or iron overload. Iron chelation therapy with Desferal prevents organ failure in MDS patients receiving regular blood transfusions and prolongs life.

Desferal is given in addition to blood infusion, and is administered by injection, typically 3 to 7 times a week. Some patients receive twice-daily subcutaneous injections of Desferal. Others receive slow intravenous infusion by way of a portable, battery-operated pump worn over a period of about 8 hours, often overnight. (*See illustration.*) Desferal can also be given by injection into muscle (intramuscular administration).



*Desferal® (Deferoxamine) Pump*

**Exjade® (deferasirox).** Deferasirox, formerly known as ICL670, is the only commercially available iron chelator drug available that is taken by mouth. Exjade was approved by the FDA in 2005 and is under review for authorization by EMEA in Europe. Exjade is taken as a once-a-day oral regimen; however, it is not a pill. Exjade tablets are dissolved in water, orange juice, or apple juice and the suspension is swallowed. Exjade is given at a dose of 20 milligrams per kilogram body weight per day. Some clinical trials have been completed and their results are being analyzed; other clinical trials are ongoing, including one in MDS patients. The manufacturer of Exjade, Novartis, has developed a program for patients called EPASS™ (Exjade Patient Assistance and Support Services), which includes prescription fulfillment, educational support, and reimbursement assistance.

## **TREATMENT OF NEUTROPENIA**

### **White Cell Growth Factors (filgrastim or Neupogen®, sargramostim or Leukine®).**

If a patient has a low white cell count and has experienced at least one infection, administration of white cell growth factors is an option. Two growth factors, granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF), are available. Both are administered under the skin between one and seven times a week. The majority (about 75%) of the patients who use G-CSF (filgrastim, Neupogen®) or GM-CSF (sargramostim, Leukine®), experience increased white cell production, which may help to reduce the likelihood of additional infection. Neupogen and Leukine do not cause major side effects, with patients only occasionally reporting rashes and bone pain. These medications have not been shown to prolong survival.

**Antibiotic Therapy.** Because white cells are not particularly amenable to transfusion, supportive care consists primarily of antibiotic therapy. Antibiotics are used to treat bacterial infections or prevent recurrence of bacterial infections.

## **TREATMENT OF THROMBOCYTOPENIA**

**Platelet Growth Factors.** At present, there is no approved growth-factor medication for patients with thrombocytopenia. Ongoing studies, however, are showing promising results: platelet counts may increase through treatment with growth factors such as interleukin-11 (IL-11), interleukin-6 (IL-6), and in particular, thrombopoietin. In addition, two experimental, or investigational, drugs that stimulate platelet production are in clinical trials and appear to significantly improve platelet counts in patients with severe thrombocytopenia: AMG 531 (being developed by Amgen) and eltrombopag, formerly SB497115 (being developed by GlaxoSmithKline).

**Platelet Transfusions.** Platelet transfusions are rarely given unless the platelet count is below 10,000 per microliter of blood (normal counts range from 150,000 to 450,000). Patients will eventually become resistant to the transfused platelets, so transfusions of new platelets would periodically be necessary.

## **ADVANCED STAGES OF MDS**

### ***Induction Chemotherapy***

Patients whose MDS has been classified as belonging to the IPSS High-Risk Group or the Intermediate-2 Risk Group have a higher probability of the MDS progressing to AML. For this reason, physicians may recommend intensive, high-dose, or induction chemotherapy that may “induce” control of MDS by killing the myelodysplastic cells. Intensive chemotherapy for MDS refers to cytotoxic (“cell-killing”) combination regimens like those used to treat AML. In addition to select High-Risk or Intermediate-2 Risk patients, intensive chemotherapy may also be appropriate for Low-Risk and Intermediate-1 Risk patients with progressive disease, 60 years of age or younger and in good physical condition.

Chemotherapy treatment has significant side effects. Commonly recognized side effects include hair loss, development of mouth sores, nausea and vomiting, and diarrhea. But besides these effects, chemotherapy adversely affects healthy cells along with the myelodysplastic cells.

Because of the loss of normal blood cells, the patient remains hospitalized for several weeks following chemotherapy while transfusions of red cells and platelets are given along with antibiotics to fight infection. If the induction chemotherapy adequately controls the myelodysplastic cells, then relatively normal blood cells should again grow within several weeks. As normal cells proliferate, the frequency of transfusions will decrease and the risk of infection will lessen.

Unfortunately, the chance of controlling MDS with induction chemotherapy is only about 30%. Even in successful cases, the disease often returns within twelve months. Thus, aggressive chemotherapy is given to a minority of MDS patients.

### ***Blood or Marrow Transplantation***

Previously called bone marrow transplantation, blood or marrow transplantation may actually involve the transfusion of progenitor blood cells (stem cells) from the bone marrow or circulating blood. Blood or marrow transplantation is synonymous with hematopoietic stem cell transplantation

and peripheral stem cell transplantation. (Peripheral stem cell refers to stem cells in the circulating, or peripheral, blood.)

Although blood or marrow transplantation offers a potential cure for MDS, this procedure is available to only a small proportion of patients due to the age of MDS patients and the lack of a suitable donor. There are also significant risks. At this time, blood and marrow transplantation for MDS is largely limited to allogeneic transplantation, in which blood from a marrow donor is transfused into a recipient (the patient). Autologous blood or marrow transplantation for MDS, in which the patient's own blood is used, may be considered in the context of a clinical trial.

Blood or marrow transplantation is recommended for patients classified as IPSS Low-Risk or Intermediate-1 Risk who have significant cytopenias and related problems and are 60 years of age or younger and in good physical condition. Recently, reduced-intensity chemotherapy regimens have been used prior to the transplantation procedure in the clinical trial setting. Such regimens have fewer side effects and therefore reduced-intensity chemotherapy may provide another option for the older patient. Blood or marrow transplantations used with reduced-intensity chemotherapy are sometimes referred to as "mini-transplants," because lower, more tolerable chemotherapy doses are used. However, there is a concern is that not all myelodysplastic cells will be killed with the reduced-intensity chemotherapy. The attractiveness of the approach is the lower incidence of side effects, which means the treatment will be better tolerated by the older patient, and the patient, being stronger, may have a greater chance of surviving the transplant. (Younger patients, who generally are more vigorous, can generally withstand the standard dose of chemotherapy that kills all myelodysplastic cells.) Studies of mini-transplants for patients 55 to 70 years old are in progress.

In addition to the short course of a combination chemotherapy regimen (either standard high-dose chemotherapy or reduced-intensity), a short course of immunosuppressive therapy prior and sometimes following the procedure is administered to prevent rejection of the donor's cells.

Numerous chemotherapeutic agents in various combinations and doses are being studied for their ability to eradicate myelodysplastic cells and for their side effects. Researchers and clinicians are anxious to find effective agents that have minimal side effects. Similarly, numerous immunosuppressive agents in various combinations and doses are being studied for their ability to reliably prevent graft rejection without leaving the patient vulnerable to infections.

To date, hundreds of MDS patients have undergone blood or marrow transplantation and almost all have been under the age of 40. Patients who survive the complications have a high probability of being cured.

## OTHER THERAPIES

### VITAMIN THERAPY

Treatment with vitamins has been an active area of MDS research over the past two decades. In test tube studies, myelodysplastic cells often normalize when exposed to vitamins such as D<sub>3</sub> and A (retinoic acid). Overall, however, clinical trials have been disappointing. Presently a major area of research is devoted to combining vitamins with low doses of chemotherapy and/or growth factors such as EPO and GM-CSF. It may be worth asking your specialist about any ongoing studies.

### EXPERIMENTAL THERAPIES

An expanding number of experimental, or investigational, drugs are being evaluated for their potential use in treating MDS. These include low-dose, or non-intensive, chemotherapy agents and many diverse types of drugs and compounds with sometimes different, sometimes overlapping modes of action. Experimental therapeutic agents, which have not yet received FDA approval for treatment of MDS, may be available to patients through clinical trials. These new agents are listed in the table, and some are discussed below. *[Please contact The MDS Foundation, Inc., for more information on these drugs or for information on clinical trials.]*

#### Experimental Therapies for MDS by Drug Class\*

##### Angiogenesis inhibitors

Trisenox<sup>®</sup> (arsenic trioxide)  
Thalomid<sup>®</sup> (thalidomide)  
Avastin<sup>™</sup> (bevacizumab)

##### Deoxyadenosine analogues

Troxatyl<sup>®</sup> (troxacitabine)  
Clolar<sup>®</sup> (clofarabine)

##### Glutathione S-Transferase Inhibitors

Telintra (TLK199)

##### Farnesyl Transferase Inhibitors

Zarnestra<sup>®</sup> (tipifarnib)  
Sarasar<sup>®</sup> (lonafarnib)

##### Immunomodulators

Thymoglobulin<sup>®</sup>, Lymphoglobulin<sup>®</sup>, Atgam<sup>®</sup> (antithymocyte globulin)

##### Topoisomerase-1 Inhibitors

Hycamtin<sup>™</sup> (topotecan)  
Orathecine<sup>™</sup> (rubitecan)

##### Tyrosine Kinase Inhibitors

PTK787/ZK222584

\* These therapies may have multiple mechanisms of action and therefore may belong to more than one drug class; see sections, "Approved Treatments for MDS" and "MDS Drug in the Pipeline," for other therapeutic agents

**Thymoglobulin®**, **Lymoglobulin®**, **Atgam®** (*antithymocyte globulin or ATG*). Antithymocyte globulin, commonly referred to as ATG, is an immunosuppressive agent that eliminates abnormally proliferating white blood cells called T lymphocytes, or T cells, that are believed to disrupt normal blood cell growth. Eliminating these T cells may restore normal red blood cell maturation in select MDS patients; thus, patients who receive ATG therapy may gain red blood cell transfusion independence. Since 2002, several relatively small clinical trials have provided encouraging findings about the use of intravenous ATG therapy in low-risk MDS patients, such as durable hematological responses and increased disease-free and overall survival.

To further study the potential benefit of ATG therapy in MDS, an international database has been created—the ADOPT Registry. (ADOPT stands for **A**TG **D**ose, **O**utcomes, & **P**atient Identification.) Physicians and clinical researchers who are treating MDS patients with ATG are encouraged to use the registry. It is hoped that analysis of patient data will aid in determining the optimal ATG dose and schedule; identifying hematologic, clinical, and quality-of-life benefits; and tracking ATG-related adverse events.

**Trisenox®** (*arsenic trioxide*). Arsenic trioxide is currently being studied as a single agent and as a component of several combination drug regimens in more than 40 clinical trials in a variety of cancers and hematologic conditions, including MDS. This drug is administered as an intravenous infusion on several days during a 28-day cycle; the dose and number of days depends on the dosing regimen.

Clinical trial results of arsenic trioxide, reported in 2004, have demonstrated favorable hematologic responses (e.g., transfusion independence) in MDS patients treated with arsenic trioxide as a single-agent therapy or in combination with thalidomide. The safety of arsenic trioxide has been amply demonstrated and this compound is approved by the FDA for the treatment of relapsed or refractory acute promyelocytic leukemia (APL), a rare, life-threatening hematologic malignancy. APL is one of eight subtypes of AML.

Arsenic trioxide is believed to have tumor-fighting activity via several molecular mechanisms, including the inhibition of new blood vessel growth to cancerous tissue (anti-angiogenesis) and the stimulation of cell death (apoptosis), a normal biological process that is affected in MDS.

**Thalomid®** (*thalidomide*). MDS and leukemia patients have elevated levels of vascular endothelial growth factors and other factors that promote new blood vessel growth, which together allow the growth and distribution of abnormal and cancerous cells. Thalidomide reduces the blood supply in the marrow, thereby working to limit the growth and spread of aberrant cells. In addition, thalidomide acts to thwart cytokines that promote premature death of progenitor cells in the bone marrow.

In clinical trials, oral thalidomide, given alone or in combination with growth factors such as G-CSF, appears to improve anemia in some patients, particularly younger patients with low-risk MDS. Rather surprisingly, studies have found that MDS patients with high serum levels of EPO who are transfusion dependent have red blood cell responses. Such patients are generally not responsive to EPO therapy and therefore thalidomide represents a therapeutic option for this subset of MDS patients.

The side effects associated with thalidomide can cause patients to discontinue therapy. The most commonly occurring side effects include sedation, constipation, and neuropathy. Older patients in particular have difficulty in tolerating thalidomide.

**Telintra™ (TLK199).** Telintra is an intravenously administered drug that works by inhibiting a key enzyme involved in cell growth and proliferation. (The enzyme is called glutathione S-transferase P1-1, or GST P1-1.) Telintra inhibits the normal activity of GST P1-1, thereby promoting normal growth and differentiation of all blood cell types.

Interim results from a multicenter phase II clinical trial in 26 evaluable patients with refractory MDS showed that the majority of patients (61.5%) had clinically significant improvement in one or more blood cell lineages (red cells, white cells, and/or platelets) and improvements were noted across the FAB subtypes RA, RAEB, RAEB-t, and RARS. Clinical responses were associated with decreased need for red blood cell and platelet transfusion and growth factor support. The drug regimen evaluated in the trial was Telintra (600 milligrams per meter squared) given as an intravenous infusion over 60 minutes daily for 5 days every 3 weeks for up to 8 cycles. Side effects of Telintra were mild and infusion-related. Ongoing clinical trials are evaluating the safety and efficacy of different formulations of Telintra.

**Hycamtin (topotecan).** Topotecan is administered intravenously as a continuous infusion, without or with other chemotherapy drugs (for example, cytosine arabinoside, also known as Ara-C). Treatment with topotecan has resulted in complete remission of MDS in some patients. However, the duration of remission is relatively short as these patients experience continuous relapses with no apparent change in survival time. In clinical trials of topotecan in combination with Ara-C, the duration of remission is about 10 months. Side effects associated with topotecan are generally manageable.

## SUMMARY

MDS is a relatively common disorder of the bone marrow, and the most common hematologic malignancy among adults. Diagnosing MDS can be difficult because of the similarities with other hematologic disorders, including AML, hypoplastic anemia, and hereditary sideroblastic anemia. However, research efforts seeking to uncover the disease mechanisms that lead to MDS are contributing to our understanding of MDS. Increased awareness and understanding of MDS, in turn, contributes to the refinement of criteria by which a diagnosis of MDS is made. Equally important, our increased understanding of the disease mechanisms is driving the discovery of new drugs to treat specific MDS subtypes and risk groups.

MDS is a puzzling, life-threatening set of bone marrow disorders for which there are no easy cures. According to a *New England Journal of Medicine* article published in 2005, MDS is one of the most challenging problems in hematology today. Only recently has the treatment for MDS expanded beyond supportive care for the relief of symptoms. It is expected that there will be a

total of three commercially available MDS drugs by the end of 2006. While more aggressive therapies, such as chemotherapy and blood or marrow transplantation, may be options for some patients, it is necessary to weigh the benefits and risks of all therapeutic approaches on an individualized basis. Side effects of some therapies may be intolerable for some patients or the side effects may negatively impact patients' quality of life. Whatever management strategy is ultimately chosen, above all it should reflect the patient's preferences.

## **ADDITIONAL INFORMATION SOURCES**

### **The MDS Foundation, Inc.**

P.O. Box 353, 36 Front Street  
Crosswicks, NJ 08515  
Tel: 800-MDS-0839 (within US only)  
609-298-1035 (outside US)  
Fax: 609-298-0590  
[www.mds-foundation.org](http://www.mds-foundation.org)

### **Aplastic Anemia & MDS International Foundation, Inc.**

P.O. Box 613  
Annapolis, MD 21404-0613  
Tel: 800-747-2820, 410-867-0242  
Fax: 410-867-0240  
[www.aamds.org](http://www.aamds.org)

### **Mia Hamm Foundation**

P.O. Box 56  
Chapel Hill, NC 27514  
Tel: 919-544-9848  
Fax: 919-544-9878  
[www.miafoundation.org](http://www.miafoundation.org)

### **Blood & Marrow Transplant Information Network**

2900 Skokie Valley Road  
Suite B  
Highland Park, IL 60035  
[www.bmtinfont.org](http://www.bmtinfont.org)

*Transfusion-Dependent Iron Overload and MDS: A Handbook for Patients.*  
The MDS Foundation, Inc. 2006.

Bennett JM (ed). *The Myelodysplastic Syndromes: Pathobiology and Clinical Management.* New York: Marcel Dekker, Inc. 2002.

Greenberg PL. *Myelodysplastic Syndromes: Clinical and Biological Advances.* New York: Cambridge University Press, 2005.

### **Iron Disorders Institute, Inc.**

P.O. Box 2031  
Greenville, SC 29602  
Information request line: 888-565-IRON (4766)  
[www.irondisorders.org](http://www.irondisorders.org)

**Iron Overload Diseases Association, Inc.**

433 Westwind Drive  
North Palm Beach, FL 33408-5123  
Tel: 561-840-8512  
website: [www.ironoverload.org](http://www.ironoverload.org)

***How to Contact The Myelodysplastic Syndromes Foundation:***

The MDS Foundation, Inc.  
P.O. Box 353, 36 Front Street  
Crosswicks, NJ 08515  
Tel: 800-MDS-0839 (within US only)  
609-298-1035 (outside US)  
Fax: 609-298-0590  
[www.mds-foundation.org](http://www.mds-foundation.org)