



UNITED STATES

Understanding Myelodysplastic Syndromes: A Patient Handbook

Sixth Edition

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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. MDS is often referred to as a “bone marrow failure disorder”. MDS is primarily a disease of the elderly (most patients are older than age 65), 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 may accumulate in the bone marrow or they may have a shortened life span, resulting in fewer than normal mature blood cells in the circulation.

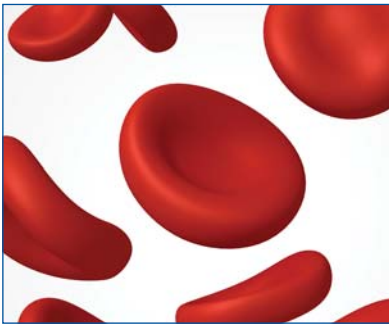
Low blood cell counts, referred to as cytopenias, are a hallmark feature of MDS and are responsible for some of the symptoms that MDS patients experience — infection, anemia, spontaneous bleeding, or easy bruising. Anemia (low red blood cell counts), neutropenia (low white blood cell counts), and thrombocytopenia (low platelet counts) are the major types of blood cell cytopenias, and are discussed below.

In addition to reduced numbers of blood cells, 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. Syndromes comes from the Greek and means a set of symptoms that occur together.

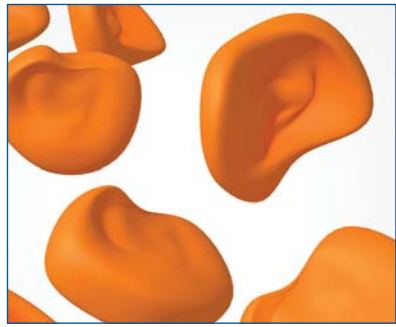
Failure of the bone marrow to produce mature healthy cells is a gradual process, and therefore MDS is not necessarily a terminal disease. Some patients do succumb to the direct effects of the disease: reduced blood cell and/or reduced platelet counts may be accompanied by the loss of the body's ability 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 normally produces mature red blood cells that carry oxygen to the body's tissues. These healthy red cells contain 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 healthy, mature red blood cells 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 ("dysplastic") red blood cells

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EFFECT ON WHITE BLOOD CELLS

In addition to red blood cells, the bone marrow produces white blood cells, which are key cells of the body's immune system that 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 (also known as granulocytes), which primarily fight bacterial infections and lymphocytes, which primarily fight viral infections.

Some 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 developed neutropenia still suffer recurrent infections. This may be a function of cell quality rather than cell quantity. Although the white blood cell count is normal, a patient's white blood cells are not able to function as well as those in a person who does not have MDS. Researchers are exploring the role of an "immunological defect" in the development of MDS.

EFFECT ON PLATELETS

Platelets are also produced by the bone marrow and are critical to blood coagulation and the formation of clots to stop bleeding. Healthy bone marrow normally manufactures between 150,000 and 450,000 platelets per microliter of blood; however, many 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 more severe 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 breast or testicular cancers, 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 or radiation 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.

Long term exposure to certain environmental or industrial chemicals, such as benzene, can also trigger MDS. While benzene use is now highly regulated, 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. There is insufficient data 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.

MDS is not inherited. In fact, it is a very rare occasion when family members, including siblings, are diagnosed with MDS.

WHAT ARE THE SYMPTOMS OF MDS?

In the early stages of MDS patients may 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 reduced platelet counts. On occasion, the white cell and platelet counts may be low while the hematocrit remains normal. 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 of the cell count.

LOW RED CELL COUNT (ANEMIA)

The majority of individuals are anemic when they are initially diagnosed with MDS. Anemia is characterized by a persistently low hematocrit (a measure of the body’s red blood cells) or persistently low levels of hemoglobin (the blood protein that carries oxygen to the body’s tissues). 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 report chronic overwhelming 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. Although chronic anemia is seldom life threatening, it can drastically reduce a patient's quality of life.

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. 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, iron content in the blood (serum ferritin levels), and the level of a substance called erythropoietin (EPO) in the serum. EPO is a protein produced by the kidneys in response to low oxygen in body tissues. This protein stimulates the production of red blood cells (also called erythrocytes) in the bone marrow.

If the blood test indicates that the red blood cells are misshapen (dysplastic), the patient could possibly have a Vitamin B₁₂ or folate deficiency. Like 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 B₁₂ and folate deficiencies as the cause of anemia, levels of these vitamins in the blood are also measured.

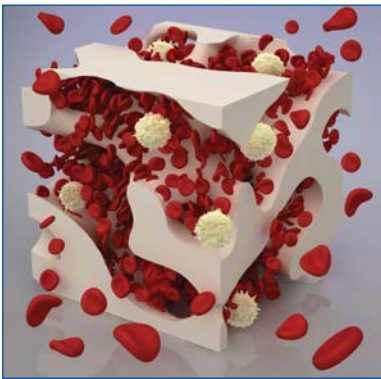
BONE MARROW EXAMINATION

Blood test results indicating that a patient is anemic, with or without a low white cell and/or a low platelet count, may prompt the physician to examine the patient's bone marrow. A bone marrow examination can reveal abnormalities in the cells of the marrow (e.g., dysplastic cells) and also chromosomal abnormalities, such as missing or extra chromosomes. These tests provide additional information that can help in establishing the diagnosis. There are two parts to a bone marrow examination: a bone marrow

aspiration, in which a sample of the liquid portion of the marrow is taken, and a bone marrow biopsy, in which a sample of the boney portion of the bone marrow is taken. Both the aspiration and biopsy are usually performed at the same time.

The physician or pathologist uses a microscope to examine the cells in the bone marrow aspirate and biopsy samples. The percentages of blasts (immature cells) and dysplastic blood cells, chromosomes are made up of DNA and are found in a cell's nucleus. Because DNA contains the instructions for making proteins and other critical biomolecules necessary for proper cell functioning, missing or damaged chromosomes can have serious consequences. The bone marrow is also tested for chromosome abnormalities, such as missing or deleted chromosomes or changed or extra chromosomes or parts of chromosomes in a blood cell.

Blood cell abnormalities are described in a report of hematologic findings and chromosome abnormalities are described in a report of cytogenetic findings. MDS patients may have periodic bone marrow exams to determine if their disease has progressed.



Healthy bone marrow



Abnormal bone marrow with dysplastic blood cells and abnormal chromosomes

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Risks of a Bone Marrow Examination

As is the case with all procedures, there are some risks that accompany a bone marrow examination; these include infection, bruising and bleeding, and discomfort. Anytime a needle is inserted through the skin, there is a possibility of infection. However, the risk of infection is highly unlikely since aseptic techniques are used and antiseptic conditions are maintained throughout the procedure.

Although many patients are anxious or fearful of undergoing 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 reality, little pain should be experienced when the bone is "pricked" since the exam is performed using local anesthesia.

Procedure Used in the Bone Marrow Examination

A bone marrow examination can be performed in the physician's office usually in about twenty minutes with the patient under mild sedation or analgesia. As the patient reclines on the examination table, either on their stomach or their side (whichever position is most comfortable), the physician locates the posterior iliac crest, a bony protrusion on the right or left back side of the hip. This site, not the spine, or breast bone, is used to obtain a bone marrow sample. The physician swabs the skin with iodine and places a sterile towel and drape over the area to prevent infection.



Cross-section of the hip

A needle, smaller than one used to draw blood from the arm, is slowly inserted under the skin to inject a local anesthetic; then a longer, slightly larger needle is used to inject an anesthetic into the bone itself. Patients commonly experience a slight burning sensation with the insertion of the first needle and 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.

After about five minutes or until the bone covering, or periosteum, is well anesthetized (additional anesthetic can be injected into the area if the patient continues to have sensation), the physician proceeds using a third, larger, specialized needle to penetrate through the dense outer shell of bone and into the bone marrow. (Since there are no nerve endings in the marrow, this stage should be painless.) Once the needle is inside the bone, the patient is asked to take several slow, deep breaths, while the center portion of the needle is removed. The physician attaches a syringe to the end of the needle and pulls out, or aspirates, the liquid portion of the marrow (about a tablespoon in total). During the aspiration, the patient typically experiences a very brief pulling sensation that may travel down their leg for just 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 larger needle is inserted to obtain a small piece of the bone for biopsy. As the needle is being inserted into the bone, the patient should feel a dull pressure or pushing sensation. When the physician loosens the bone and removes it, the patient experiences a jerking sensation. As with bone marrow aspiration, the biopsy takes only a few minutes.

At the completion of the bone marrow exam, since the skin cut for the procedures is usually very small, no stitches are necessary and only a pressure bandage is applied. Some patients may develop a bruise or swelling under the skin, particularly those whose platelet count is low.

Mild pain or discomfort may be experienced at the procedure site for two to three days after the bone marrow exam. For safety reasons, the patient should have a friend, family member, or care taker travel home with them; the patient should not drive.

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 distinct MDS subtypes based on large, worldwide patient data sets and increased understanding of the disease processes involved in MDS.

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

Another system that describes the progression of MDS and the prognosis for the patient is the International Prognostic Scoring System (IPSS). This system is currently being reviewed to increase its accuracy in choosing treatment for MDS patients.

FRENCH-AMERICAN-BRITISH (FAB) CLASSIFICATION

The FAB Classification was developed in the early 1980s by a group of physicians with expertise in diagnosing MDS. These experts were from France (F), America (A), and Great Britain (B); 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 MDS subtypes recognized by the WHO classification system are highlighted in the table.

RA/RARS: Refractory anemia (RA) and with refractory anemia ringed sideroblasts (RARS). Patients in these categories have anemia that is refractory, or not responsive, 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 and contain iron deposits in a “necklace” pattern.

Refractory anemia with or without ringed sideroblasts (RA and RARS) are considered the most benign subtypes in the WHO classification system. Under this system, MDS patients with RA or RARS 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 (low white cells) or refractory thrombocytopenia (low platelet count) 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 subtypes, 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.

5q- (5q minus) syndrome. A deletion of a portion of the 5q chromosome or 5q minus (5q-) is now recognized as a true MDS subtype and was originally described more than 30 years ago. A deletion within the long arm of chromosome #5 may 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-.

Patients with 5q- have refractory anemia that requires supportive care. The syndrome usually occurs in women, with mild to moderate degrees of anemia and low white blood cell counts (leukopenia), and often with normal to elevated platelet counts.

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).

| WHO Classification of MDS | |
|--|---|
| MDS Subtype | Description |
| Refractory anemia (RA) | |
| <ul style="list-style-type: none"> ● <i>Without ringed sideroblasts (RA)</i> ● <i>With ringed sideroblasts (RARS)</i> | <p>Minimal dysplasia in one blood cell type (red blood cells or erythrocytes) and less than 5% blasts in the bone marrow</p> <p>Same RA plus more than 15% ringed sideroblasts in the bone marrow</p> |
| Refractory cytopenia with minimal dysplasia (RCMD) | |
| <ul style="list-style-type: none"> ● <i>Without ringed sideroblasts (RCMD)</i> ● <i>With ringed sideroblasts (RCMD-RS)</i> | <p>Dysplasia (greater than 10%) in 2 or 3 blood cell types and less than 5% blasts and less than 15% ringed sideroblasts in the bone marrow</p> <p>Same as above plus more than 15% ringed sideroblasts</p> |
| RA with excess blasts (RAEB) | |
| <ul style="list-style-type: none"> ● <i>RAEB-1</i> ● <i>RAEB-2</i> | <p>Presence of 5% to 9% bone marrow blasts</p> <p>Presence of 10% to 19% bone marrow blasts</p> |
| 5q- syndrome | Patients with no chromosome abnormality other than a deletion in the long arm of chromosome #5 |
| Unclassified MDS | Includes patients with single blood cell type cytopenia other than anemia (i.e., neutropenia or thrombocytopenia) and unusual features (e.g., marrow fibrosis) |

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. This is termed "prognosis". The IPSS Score is a score assigned to certain values. First, the percentage of blasts in the bone marrow, second, the cytogenetic findings (identification of chromosomal abnormalities) in bone marrow blood cells, and third, the blood cell counts and other blood test findings.

Determining the IPSS Score

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

| Blasts in Bone Marrow | Score Value |
|------------------------------|--------------------|
| 5% or less | 0.0 |
| 5–10% | 0.5 |
| 11–20% | 1.5 |
| 21–30%* | 2.0 |

| Cytogenetic Finding† | Score Value |
|-----------------------------|--------------------|
| Good | 0.0 |
| Intermediate | 0.5 |
| Poor | 1.0 |

| Blood-test Findings‡ | Score Value |
|-----------------------------|--------------------|
| 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).

† "Good" cytogenetics include: 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" cytogenetics include: Other than "Good" or "Poor" "Poor" cytogenetics include: Loss of one of the two #7 chromosomes ("monosomy 7"), addition of a third #8 chromosome ("trisomy 8"), or three or more total abnormalities.

‡ 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 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.

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.) Your physician will recommend a treatment program based on your overall health and medical history (“performance score”), 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 | | |
|---|----------------------|------------------|
| Parameter (units) | Normal Result | My Result |
| 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% | _____ |
| Cytogenetic findings* | | |
| (Good, Intermediate, Poor) | Good | _____ |
| WHO classification | Not applicable | _____ |
| FAB classification | Not applicable | _____ |
| IPSS classification | Not applicable | _____ |
| Vitamin B ₁₂ 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, and pre-existing conditions. Several treatment options are available to MDS patients; however, not all options are appropriate for every MDS patient.

In children and younger patients, the availability of a suitable (preferably related) marrow donor for possible bone marrow transplantation (also called hematopoietic stem cell transplantation) may be considered since this is the only curative treatment currently available for MDS.

Numerous drug therapies continue to be investigated for their ability to either eradicate or suppress the abnormal dysplastic blasts in the bone marrow and/or to stimulate maturation of healthy cells.

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

- supportive care, which includes (1) the use of red blood cell transfusions to manage the symptoms of anemia and iron chelation therapy to manage iron overload, (2) platelet transfusions for thrombocytopenia, and (3) antibiotics to fight persistent or recurrent infections
- myeloid (blood) growth factors (like erythropoietin) to stimulate healthy blasts in the bone marrow to produce red and white blood cells, as well as platelets
- new drug therapies for MDS that target one or more underlying biologic mechanisms involved in the development of myelodysplasia

GOALS OF TREATMENT

For the vast majority of MDS patients the goals of treatment include, improving anemia, controlling persistent or recurring infections, controlling excessive bruising and bleeding, improving quality of life, and prolonging survival.

Since most patients with MDS experience symptoms of anemia, relief from overwhelming fatigue and lethargy is an important treatment goal. Along with the physical symptoms accompanying anemia, there can be a psychological toll as well. Patients who are too tired to engage in daily living activities or too tired to get out bed are likely to become depressed after a period of time.

Anemia can be treated with red blood cell transfusions and anemic MDS patients who require multiple red blood cell transfusions are termed “transfusion-dependent”. Repeated transfusions have an obvious negative impact on a patient’s quality of life — additional doctor or clinic visits — and repeated transfusions may also have a negative impact on disease progression and survival. Transfusion *independence* is, therefore, a major goal of treatment. Several relatively new drug therapies that reduce or eliminate this transfusion need in MDS patients with symptomatic anemia are now available. Treatment with growth factors and drugs, such as azacitidine (Vidaza[®]), decitabine (Dacogen[®]), and lenalidomide (Revlimid[®]), has resulted in transfusion independence for many MDS patients.

TREATMENT OPTIONS FOR MDS

Supportive Care

The standard of care for MDS patients is largely supportive care, which includes red blood cell transfusions for the treatment of anemia, antibiotic therapy for the treatment of infection, and platelet transfusions for the treatment thrombocytopenia.

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 IPSS Low or Intermediate-1 Risk groups 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, and/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 or “iron overload”. This can be a potentially dangerous condition since the human body cannot eliminate excess iron and the iron accumulates in organs like the liver and heart. Fortunately, it can be treated with iron-chelating drugs (see below). For more information on iron overload and its treatment, contact the Myelodysplastic Syndromes Foundation.

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 administration of a diuretic like 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 is available for patients who receive regular blood transfusions for their anemia (see below).

Induction Chemotherapy

Patients whose MDS has been classified as belonging to the IPSS High or Intermediate-2 Risk Group have a higher probability of disease progression 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. Induction or intensive chemotherapy for MDS refers to cytotoxic (“cell-killing”) combination regimens like those used to treat AML.

In addition to select High or Intermediate-2 Risk patients, intensive chemotherapy may also be appropriate for Low- 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. Numerous chemotherapeutic agents in various combinations and doses are being studied for their ability to treat MDS and to understand the side effects of these drugs. Researchers and clinicians are anxious to find effective agents that have minimal side effects.

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.

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 prescription drugs approved by the U.S. Food & Drug Administration (FDA) for the treatment of transfusion-dependent iron overload: deferoxamine (Desferal®) and deferasirox (Exjade®). Deferasirox and another iron chelator, deferiprone (Ferriprox®), are licensed for use in Europe and other countries for patients with iron overload.

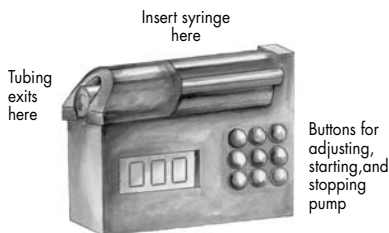
Iron chelation therapy has been shown to improve overall survival in transfusion-dependent MDS patients. In the US, the National Comprehensive Cancer Network (NCCN) guidelines recommend that patients who receive more than 20 to 30 units of red blood cells receive iron chelation therapy and the MDS Foundation's Chelation Therapy Guidelines recommend that MDS patients who have serum ferritin levels greater than 1,000 nanograms per milliliter or have received more than 20 units of red blood cells should receive iron chelation therapy and be monitored regularly, especially those with low-risk disease. Similar recommendations are made in the European treatment guidelines for MDS.

Desferal® (deferoxamine)

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

Deferoxamine 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 deferoxamine. 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.) Deferoxamine can also be given by injection into muscle (intramuscular administration).



Continuous infusion pump for administering Desferal® (Deferoxamine)

Exjade® (deferasirox). Deferasirox is the only commercially available iron chelator drug available that is taken by mouth. Deferasirox is approved by both the FDA and the European drug regulatory agency (European Agency for the Evaluation of Medicinal Products, or EMEA). Deferasirox is taken orally once-a-day. The tablets are dissolved in water, orange juice, or apple juice and the patient drinks the liquid. Deferasirox is typically given at a starting dose of 20 milligrams per kilogram body weight per day. A phase II clinical trial has shown that deferasirox significantly reduced iron overload in patients with Low or Intermediate-1 risk MDS after treatment for one year. This ongoing trial will further evaluate the impact of deferasirox on survival. Other trials that are in progress are examining the long-term safety of deferasirox use and the effects of dosing adjustments on serum iron levels. The manufacturer of deferasirox, Novartis, has developed a program for patients called EPASS™ (**Exjade Patient Assistance and Support Services**), which includes prescription fulfillment, educational support, and reimbursement assistance.

Ferriprox® (deferiprone). Deferiprone is an oral iron chelator licensed for use in European and other non-US countries for patients with iron overload who are unable to use deferoxamine because of intolerability or lack of effectiveness. In clinical studies and in clinical practice, deferiprone has been shown to be effective in removing iron from the body. Deferiprone has a side effect profile similar to that of deferoxamine, and is being evaluated alone and in combination with deferoxamine in clinical trials in the US in transfusion-dependent patients with iron overload.

| Chelation Therapy for Iron Overload | | | |
|-------------------------------------|---|------------|-------------------|
| | Iron Chelator | | |
| Property | Desferal | Exjade | Ferriprox |
| Route of Administration | Intramuscular (IM) Subcutaneous (SC) | Oral | Oral |
| Total Daily Dose* | 10–20 (IM) 20–40 (SC) | 20–30 | 75–100 |
| Dosing | 8–12 h, 5–7 d/wk (SC) | Once daily | Three times daily |

*milligrams per kilogram body weight

Antibiotic Therapy

Because white cells do not respond well when given as a transfusion, supportive care consists primarily of antibiotic therapy. Antibiotics are used to treat bacterial infections or prevent recurrence of bacterial infections.

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) since patients will eventually become resistant to the transfused platelets. So transfusions of new platelets are given periodically only as necessary.

Pyridoxine (Vitamin B₆)

If the bone marrow stain from a bone marrow biopsy shows deposits of iron in the red blood cells — an indication of sideroblastic anemia — then it is recommended that the patient try taking 100 mg of vitamin B₆ 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 B₆ 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. Note that pyridoxine doses exceeding 100 mg twice daily can produce side effects such as tingling of the fingers.

BLOOD CELL GROWTH FACTORS

Erythropoietin or EPO (Epogen[®], Procrit[®]) and Darbepoietin (Aranesp[®]). 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 likely to benefit patients whose natural (blood serum) EPO level is below 500 International Units per liter and who do not need frequent transfusions. Patients who are unresponsive to EPO alone 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 IPSS Low- or Intermediate-1 risk groups.

Recombinant EPO, epoietin, is available as two different brand-name drugs: Epogen[®] and Procrit[®]. Darbepoetin (Aranesp[®]) is related to, but a different form of, erythropoietin that is longer acting. Darbepoetin has a more convenient dosing schedule (once-weekly) than Epogen[®] and Procrit[®] (three times weekly) and, like these drugs, is most effective in patients with low-risk MDS that have low blood serum EPO levels (<500 Units per liter). All three drugs have been shown to increase red cell counts in MDS patients. A systematic review of studies from 1990 to 2008 in MDS patients treated with epoietin or darbepoetin found similar red blood cell response rates for the two different forms of EPO (57.6% and 59.4%, respectively).

In 2007, the FDA issued an advisory about the safety of epoietin and darbepoetin use in patients with cancer who were anemic but not undergoing active treatment with chemotherapy. The FDA also made recommendations for the use of these products in cancer patients and revised the labeling for these products. It is important to note that the affected patients ***did not have MDS and the studies that were used to support these changes are viewed by most clinicians as flawed or inconclusive.***

These products have been safely used in a large number of MDS patients and long-term data have not shown any negative effect on either survival or progression to AML. One recent study in MDS patients compared 121 patients treated with EPO plus G-CSF with 237 untreated patients and showed a 39% response in the EPO plus G-CSF group. There was no difference seen in the conversion rate to acute myeloid leukemia (AML) between the two groups and the authors concluded that treatment of anemia in MDS

with an EPO plus G-CSF may have a positive impact on outcome in patients with no or low transfusion need, while not affecting the risk of leukemic transformation (Jädersten, 2008). Medical societies, such as the American Society of Clinical Oncology and the American Society of Hematology, as well as the National Comprehensive Cancer Network's treatment guidelines for MDS, continue to recommend the use of epoetin and darbepoetin for the management of symptomatic anemia in MDS patients but target hemoglobin levels to less than or equal to 12 grams per deciliter.

Filgrastim (Neupogen®) and Sargramostim (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. Filgrastim and sargramostim do not cause major side effects, with patients only occasionally reporting rashes and/or bone pain.

Oprelvekin (Neumega®). Oprelvekin, a recombinant platelet growth factor, is approved for the treatment of patients with severe thrombocytopenia. Oprelvekin increases platelet production by stimulating the growth of immature platelets in the bone marrow. Oprelvekin has limited activity in some MDS patients. In a phase II study of 32 MDS patients receiving oprelvekin at a dose of 10 micrograms/kilogram/day, 9 patients (28%) had increases in their platelet count, but only 5 of these platelet responses were clinically meaningful. The increase in platelet counts lasted an average of 9 months. Oprelvekin use is associated with side effects, the more common being edema, malaise, and low-grade fevers, which are problematic for MDS patients with symptomatic anemia.

Romiplostim (Nplate™). Romiplostim (Nplate™) has recently received FDA approval for thrombocytopenia in patients with chronic immune thrombocytopenia purpura, a disorder characterized by increased platelet destruction or inadequate platelet production. Romiplostim is a recombinant protein given by subcutaneous injection weekly. It belongs to a class of drugs known as thrombopoietin-receptor agonists, and works by stimulating these receptors located on specific cells in the bone called megakaryocytes, which leads to increased platelet counts. In a study of low-risk MDS patients with thrombocytopenia, romiplostim produced a durable platelet response in 18 (41%) of patients that lasted an average of 23 weeks. Several ongoing phase II studies in MDS patients are evaluating the benefit of romiplostim on thrombocytopenia. At present, it is not recommended for use in patients with blood cancer or a precancerous condition such as MDS. Romiplostim may worsen the condition.

Eltrombopag (Promacta®). Eltrombopag (Promacta®) is currently in clinical trials and also belongs to the class of drugs known as thrombopoietin-receptor agonists, working to stimulate receptors located on the megakaryocytes to increase platelet counts. It appears to significantly improve platelet counts in patients with severe thrombocytopenia. Eltrombopag is administered orally as a tablet once daily and is currently in phase III clinical trials for the treatment of patients with chronic idiopathic thrombocytopenic purpura.

FDA-APPROVED TREATMENTS FOR MDS

Vidaza® (azacytidine). Azacytidine was the first drug approved by the FDA specifically to treat MDS. In Europe, azacytidine has been given orphan drug status by the EMEA. (Orphan drugs are considered investigational but allowed to be used in the treatment of patients because no approved treatment for the condition is available.) Azacytidine is approved for use in patients with any MDS subtype. It is administered by subcutaneous (under the skin) or by intravenous injection. The intravenous and subcutaneous dosing schedules are the same. An oral formulation, which has been granted fast track status by the FDA, is being developed and has entered clinical trials.

Several clinical trials showed that, compared with patients who did not receive azacytidine, MDS patients treated with one subcutaneous injection of azacytidine 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 azacytidine. In some clinical trials, the time to onset of AML was significantly delayed in azacytidine-treated patients when compared with patients who did not receive azacytidine. Results of a large phase III study in 358 high-risk MDS patients (IPSS of Intermediate-2 or High) showed that compared with conventional care (either low dose chemotherapy plus supportive care or standard chemotherapy plus supportive care), treatment with azacytidine significantly prolonged overall survival (24.4 months versus 15 months). More convenient dosing schedules (5-day subcutaneous schedules) and a short intravenous infusion for azacytidine are being investigated in ongoing studies. Interim results of the study of 5-day subcutaneous dosing schedules show similar responses for hematological improvement and red blood cell transfusion independence compared with that seen with the FDA approved 7-day regimen. Azacytidine belongs to a class of drugs called DNA hypomethylating agents. Azacytidine reduces the methylation of DNA (i.e., the addition of a methyl chemical group to a DNA molecule). DNA methylation is involved in turning-off certain genes that contribute to the development of cancer (e.g., the so-called tumor suppressor genes). Azacytidine, by reducing DNA methylation, results in turning the tumor suppressor genes in MDS back on and suppressing MDS.

Revlimid® (lenalidomide). Lenalidomide is approved in the U.S for anemic MDS patients with Low- or Intermediate-1 risk MDS, particularly those with 5q- who are transfusion-dependent. Lenalidomide is taken orally and is available in capsule form.

The findings of a landmark study in MDS patients with symptomatic anemia and chromosome 5q deletion treated with lenalidomide showed that 67% of patients who were initially red blood cell transfusion-dependent achieved transfusion independence, and another 9% had their transfusion requirement decreased by 50% or more. Also, a complete cytogenetic response (i.e., chromosome abnormalities were no longer detectable) was achieved in 45% of patients. In this study, the response to lenalidomide was rapid, with an average time to response of 4.6 weeks and durable. Most of the patients received continuous daily dosing with 10 mg of lenalidomide.

Most patients participating in the study experienced neutropenia and thrombocytopenia. Some patients experienced side effects, such as rash, itching, fatigue, diarrhea, and nausea. Because lenalidomide is an analog (chemical look-alike) of thalidomide, there is a slight potential for birth defects with its use. Because of this potential, the manufacturer of lenalidomide, Celgene Corp., has set up a restricted distribution program called RevAssistSM. Only patients that enroll in and meet all of the conditions of the program are able to receive the drug.

In a study of MDS patients *without* chromosome 5q-, lenalidomide was shown to reduce the red blood cell transfusion need in 43% of patients and eliminate the transfusion need in 26% of patients. The majority of patients had a heavy transfusion burden (two or more red blood cell units/month). These findings suggest that lenalidomide may offer an alternate therapeutic strategy for patients with MDS who do not benefit from treatment with red blood cell growth factors, a hypothesis being investigated in an ongoing study.

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

Dacogen® (decitabine). Decitabine is approved in the U.S. for use in all MDS subtypes and Intermediate-1, Intermediate-2, and High-risk IPSS groups. In Europe, decitabine has orphan drug status. It is administered by continuous intravenous injection. Positive findings from a major phase III clinical trial that compared decitabine with supportive care in MDS patients revealed that of 170 patients with intermediate to high-risk MDS who participated in the trial, a significantly higher overall response rate was seen in patients receiving decitabine with the responses lasting for about 10 months: 17% response for decitabine-treated patients versus 0% for patients receiving standard of care. Patients who responded to decitabine became or remained transfusion-independent. In addition, patients who had a response (complete or partial) to decitabine had a longer time to progression to AML and extended survival compared with patients receiving supportive care alone. More convenient dosing regimens for decitabine are being evaluated in MDS patients with Intermediate-1, Intermediate-2, and High IPSS scores. Results of a randomized study of 95 patients that examined three different dosing schedules of decitabine found that patients given 20 milligrams per meter squared intravenously over 1 hour daily for 5 days, and repeated every 4 weeks had significantly more complete responses (39%) compared with the two other dosing regimens (21%–24%). Another study of 99 patients found this same dosing regimen to be clinically effective and safe.

Decitabine, (also called 5-deoxyazacytidine), is a DNA hypomethylating agent like azacytidine and works like azacytidine. In other words, decitabine reduces DNA methylation, and restores the normal functioning of tumor suppressor genes in MDS.

BLOOD OR MARROW TRANSPLANTATION

Previously called bone marrow transplantation, blood or marrow transplantation involves the transfusion of progenitor blood cells (stem cells) from a donor's bone marrow or circulating blood or from umbilical cord 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.)

Blood or marrow transplantation is preceded by a relatively short course of a cancer chemotherapy regimen (either standard high-dose or intensive chemotherapy or reduced-intensity chemotherapy). Intensive chemotherapy is called myeloablative, meaning that the patient's bone marrow cells are destroyed. It is necessary to destroy these cells (eradicate the MDS cells) prior to transfusing the new, healthy donor cells into the patient. Reduced-intensity, or non-myeloablative, chemotherapy is discussed below. A short course of immunosuppressive therapy prior to, and sometimes after, the procedure is administered to the recipient patient to prevent rejection of the donor's cells.

Although blood or marrow transplantation offers a potential cure for MDS, this procedure is available to only a small proportion of adult MDS patients due to advanced age and the lack of a suitable donor. There are also significant risks with this procedure. 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 patient. Ideally, marrow from a matched related donor (a relative with matching blood type and blood antigens, i.e., histocompatible) is used. However, marrow from an unrelated donor with matching blood type and blood antigens may be used, although the results of such transplants are generally not as successful as those in which the donor and recipient are related. Blood antigens from potential donors and recipient are examined for compatibility ("a match") using HLA — human leukocyte antigen — testing. 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- or Intermediate-1 Risk who have significant cytopenias and related problems, who are less than 60 years of age, in good physical condition, and who have not responded to other MDS treatments. Some patients classified as IPSS Intermediate-2 or High Risk may be candidates for transplantation, particularly if they are candidates for induction chemotherapy (see below).

Reduced-intensity chemotherapy regimens used prior to the transplantation procedure may offer a greater number of MDS patients the chance of a cure. Reduced-intensity chemotherapy regimens with blood or marrow transplantation (sometimes called "mini" transplants) are being investigated in the clinical trial setting. These reduced-intensity transplants have fewer side effects and may provide another option for older patients. However, there is a concern that not all myelodysplastic cells will be killed with the reduced-intensity chemotherapy and there is a higher risk of relapse. 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 may have a greater chance of a successful transplant. (Younger patients, who generally are more vigorous, can

generally withstand the standard dose of chemotherapy that kills all myelodysplastic cells.) At this time, reduced-intensity allogeneic hematopoietic stem cell transplantation is being evaluated in clinical trials.

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. For more information on bone or marrow transplantation, contact The Myelodysplastic Syndromes Foundation.

ARE THERE OTHER THERAPEUTIC APPROACHES?

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 D₃ 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. While there are many new experimental therapies with new targets, such as farnesyl transferase inhibitors, glutathione s-transferase inhibitors, tyrosine kinase inhibitors, and histone deacetylase inhibitors, some therapies are not exactly new, but they continue to be studied because they hold promise. One example is the immunomodulator, antithymocyte globulin (Thymoglobulin®, Atgam®), which is effective in select patients with specific characteristics, namely a short duration of transfusion dependence, the HLADR15 phenotype, and age less than 60. Together these agents form a diverse array of drugs and compounds with sometimes different, sometimes overlapping modes of action.

The approach to treatment of MDS is evolving. In addition to therapeutic approaches using a single agent from one drug class, various combinations of drugs from different classes are being investigated. An example of a drug combination currently under investigation in clinical trials is azacitidine and the histone deacetylase inhibitor, MS-275. By using combinations of drugs that act at more than one target site, it is hoped that a more effective treatment than any one of the agents used alone will be produced. Experimental therapeutic agents, which have not yet received FDA approval for treatment of MDS, may be available to patients through clinical trials. Some of these agents, which have shown promise in the treatment of low- and high-risk MDS, are listed in the table. *[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® (arsenic trioxide); Thalomid® (thalidomide); Avastin™ (bevacizumab)

Apoptosis Regulation

p38α MAPK (SCIO-469); Bcl-2 family BH3-binding Groove Inhibitor (obatoclax, GX15-070)

Cytokine Inhibitors

Enbrel™ (etanercept); Remicade™ (infliximab)

Deoxyadenosine analogues

Troxatyl® (troxacitabine); Clolar® (clofarabine)

Farnesyl Transferase Inhibitors

Zarnestra® (tipifarnib); Sarasar® (lonafarnib)

Glutathione S-Transferase Inhibitors

Telintra (TLK199)

Histone Deacetylase Inhibitors

MS275; Valproic acid; MG0103 (MGCD0103);
SAHA (vorinostat, suberoylanilide hydroxamic acid)

Immunomodulators

ATG-Fresenius S, Thymoglobulin®, Lymphoglobulin®, Atgam® (antithymocyte globulin)

Topoisomerase-1 Inhibitors

Hycamtin™ (topotecan); Orathecin™ (rubitecan)

Tyrosine Kinase Inhibitors

PTK787/ZK222584 (vatalanib)

* These therapies may have multiple mechanisms of action and therefore may belong to more than one drug class.

SUMMARY

Today, treatment of MDS has expanded beyond supportive care for the management of symptoms to three FDA-approved treatments within the last four years. There have been major advances in the understanding of the disease mechanisms leading to the development of MDS as well as progress in identifying patient characteristics and those patients most likely to benefit from a particular therapy. Despite these advances, a curative option is not available to all patients. Nevertheless, many more experimental therapies are being investigated in more than 400 ongoing clinical trials worldwide.

In choosing a treatment option, 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 a patient's quality of life. Whatever treatment strategy is ultimately chosen, above all it should reflect the patient's preferences and consideration of quality of life. The disease burden for MDS patients includes the need for frequent blood work, blood transfusions with red cells or platelets, physician visits, and treatments, as well as debilitating fatigue which can lead to depression.

Today, there is recognition of the tremendous impact MDS has on those living with this disease. Not only are there a daunting array of physical and medical issues — age, comorbid conditions, fatigue, shortness of breath, infection, bleeding, and complications of treatments — but also there are emotional, psychological, economic, and social burdens as well. Recognition of the enormous disease burden by health care providers has led not only to improved communication with patients but also to improved quality of care for patients living with MDS.

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
Website: www.mds-foundation.org

European Office

Sophie Wintrich
The Rayne Institute
Denmark Hill Campus
123 Coldharbour Lane
London SE5 9NU UK
Tel: +44 (0) 20 7733 7558
Fax: +44 (0) 7733 7558

American Cancer Society

Tel: (800)-ACS-2345
Website: www.cancer.org

American Society for Blood and Marrow Transplantation

85 West Olgonquin Road
Suite 550
Arlington Heights, IL 60005
Tel: 847-427-0224
Fax: 847-427-9656
Website: mail@asbmt.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
Website: www.aamds.org

Blood & Marrow Transplant Information Network

2310 Skokie Valley Road
Suite 104
Highland Park, IL 60035
Tel: 888-597-7674
847-433-3313
Fax: 847-433-4599
Website: www.bmtinfont.org

Blood & Marrow Transplant Resources

MGC Publications
1208 East Hermitage Road
Bayside, WI 53217
Tel: 414-352-3219
E-mail: mytransplant@sbcglobal.net

Bone Marrow and Cord Blood Transplantation

<http://bloodcell.transplant.hrsa.gov/>

Iron Disorders Institute, Inc.

2722 Wade Hampton Blvd.
Suite A
Greenville, SC 29615
Information request line:
888-565-IRON (4766)
Website: www.irondisorders.org

Iron Overload Diseases Association, Inc.

P.O. Box 15857
North Palm Beach, FL 33416-5857
Tel: 866-768-8629
561-840-8512
Website: www.ironoverload.org

Mia Hamm Foundation for Bone Marrow Transplant

P.O. Box 56

Chapel Hill, NC 27514

Tel: 919-544-9848

Fax: 919-544-9878

Website: www.miafoundation.org

National Marrow Donor Program

3001 Broadway Street, N.E., Suite 100

Minneapolis, MN 55413-1753

Tel: 800-627-7692

E-mail: patientinfo@nmdp.org

The Leukemia & Lymphoma Society

1311 Mamaronek Avenue

White Plains, NY 10605

Tel: 800-955-4572

914-949-5213

Fax: 914-949-6691

Website: www.leukemia-lymphoma.org

NORD (National Organization of Rare Disorders)

55 Kenosia Avenue

P.O. Box 1968

Danbury, CT 06813-1968

Tel: 203-744-0100, 800-999-6673

Fax: 203-798-2291

E-mail: orphan@rarediseases.org

Other Resources:

Transfusion-Dependent Iron Overload and MDS: A Handbook for Patients.

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Raza A; Mundle SD (ed). *Myelodysplastic Syndromes & Secondary Acute Myelogenous Leukemia: Directions for the New Millennium.* Springer Science+Business Media, Inc. 2001.

How to Contact The Myelodysplastic Syndromes Foundation:

In the US contact the MDS Foundation Patient Liaison:

Audrey Hassan

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

Website: www.mds-foundation.org

In Europe contact the MDS Foundation Patient Liason:

Sophie Wintrich

The Rayne Institute, Denmark Hill Campus

123 Coldharbour Lane

London SE5 9NU UK

Tel: +44 20 7733 7558

European Patient Advocacy Groups:

UK: MDS UK, David Hall

France: CCM, Sarah Jenny

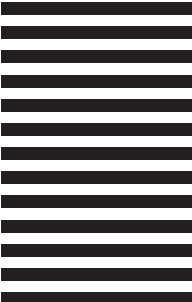
Germany: DLH, Anita Waldmann

Swedish: Blodcancer forbundet

Czech Republic: Bohumir



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Crosswicks, NJ 08515



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