A SCIENCE WRITER'S GUIDE TO BLOOD CANCERS AND RELATED DISORDERS

MODULE ONE

MYELODYSPLASTIC SYNDROMES

PREFACE

Blood cancers and related disorders – a serious health risk

In a 2003 address to the U.S. Senate Committee on Appropriations of Funding, George Dahlman, vice president of the Leukemia and Lymphoma Society, called blood cancers "a serious health risk to all Americans."[1] Despite recent progress in diagnosis and treatment of blood-related malignancies, their incidence is on the rise, and they collectively cause more deaths than all other cancers, except for cancer of the lungs.[1]

The World Health Organization has classified over 20 cancers that affect one or more components of the blood.[2] Leukemias (all types combined) and non-Hodgkin's lymphoma are the most common and the most familiar hematologic malignancies, with a combined annual rate of approximately 90,000 new cases per year in the United States.[3-5] However, lesser known forms of blood cancer such as multiple myeloma (MM) represent a significant cause of cancer-related morbidity and mortality in the United States.[6, 7] MM ranks as the third most prevalent blood cancer after non-Hodgkin's lymphoma and the combined leukemias and is responsible for over 11,000 U.S. deaths each year.[7,8]

Related blood disorders, such as myelodysplastic syndromes (MDS), also have a significant impact. The incidence of MDS is comparable to that of chronic lymphocytic leukemia, one of the most common forms of leukemia.[9] In its most aggressive form, MDS can lead to death within one year of diagnosis.[10]

With greater understanding of the underlying pathology of blood cancers and related disorders, and the introduction of new therapeutic options, the outlook for some of these diseases has improved over the past several decades.[4] Still, as George Dahlman emphasized, research into new and improved treatments must remain a priority.[1]

Purpose of this guide

This guide has been developed to help health and science writers prepare to cover important news about blood cancers and related disorders. Given the complexity and range of the subject matter, the guide will present comprehensive information about individual diseases in a modular fashion, with an emphasis on types that are less familiar. The first module focuses on MDS. Additional modules on MM and other forms of blood cancer will be added over the coming months, and existing modules will be updated periodically as important new information becomes available.

MODULE 1 – MYELODYSPLASTIC SYNDROMES

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OVERVIEW OF MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDS) are a group of similar blood disorders in which the bone marrow does not function properly and fails to produce enough healthy blood cells. While generally not characterized as a form of cancer, advanced stages of MDS may be associated with the appearance of malignant cells; in some patients, these malignant cells may progress to leukemia. MDS is one of the most common blood disorders in elderly Americans today and is likely to increase in prevalence as the elderly population continues to grow.[3,6,11,12]

The term "myelodysplastic" describes both the type of blood cells affected (*myeloid* cells) and the effect the disorders have on these cells: *dysplasia* means "abnormal formation." In MDS, the cells that give rise to red blood cells, white blood cells and/or platelets fail to develop normally, resulting in low numbers of mature blood cells, or cytopenias.

MDS at a Glance

- Affect all ages, but primarily older adults
- 12,000 to 15,000 new cases are diagnosed each year[11]
- MDS patients with chronic anemia require frequent blood transfusions
- Survival time is less than one year in patients with most severe forms of MDS[10]
- Majority of patients die from complications of blood cell deficiencies[13]
- Progress to acute leukemia in up to 30 percent of cases[6]

MDS imposes a tremendous burden on patients. Blood cell deficiencies cause a wide array of highly debilitating symptoms – such as increased susceptibility to infections, extreme fatigue and excessive bruising and bleeding – that can become life-threatening as the disease progresses. Many patients with MDS experience severe, chronic anemia, requiring red blood cell (RBC) transfusions as frequently as every two weeks. In addition to disrupting and diminishing quality of life, frequent transfusions are associated with an increased risk of iron overload, transfusion reactions and infection from agents transmitted through the transfused blood.[14, 15]

In addition, MDS may progress to acute myeloid leukemia (AML) – a disease that is difficult to treat and has a poor prognosis – in up to 30 percent of cases.[6] Even in the absence of progression to leukemia, the majority of MDS patients succumb to complications of blood cell deficiencies.[13] The most severe forms of MDS are associated with survival times of less than one year.[10]

Treatment for MDS has been limited. Chemotherapies that are effective for some forms of blood cancer result in only short-lived remission in MDS patients.[16] Transplantation of bone marrow from a healthy donor can achieve lasting remission in patients with MDS, but the risks associated with this procedure make it an impractical option for most patients.[13, 17]

But there is hope. Researchers are gaining a greater understanding of the underlying pathology of MDS, and various new treatment options are currently being studied that may help improve symptoms in patients with these disorders.

PRODUCTION AND FUNCTION OF BLOOD CELLS

In order to understand the underlying pathology and clinical course of MDS, it is important to first understand the process of blood cell production and the roles different blood cells play in maintaining health.

Components of blood

Blood is composed of several types of specialized cells that circulate in plasma, a straw-colored fluid. Major functions of blood include delivering oxygen and nutrients to tissues throughout the body, fighting infection and clotting.

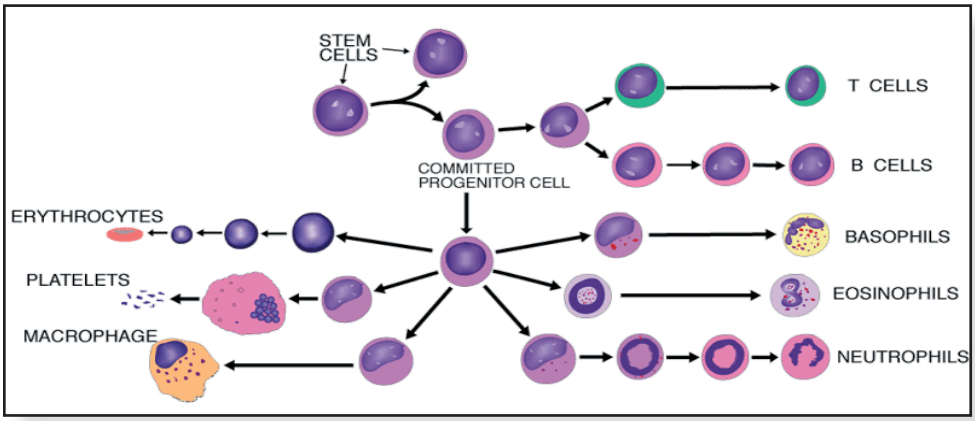
The blood cells responsible for transporting oxygen are called erythrocytes, or red blood cells. Leukocytes, or white blood cells, make up the infection-fighting, or immune component, of blood and comprise many different cell types, including neutrophils. Platelets (thrombocytes) form blood clots.

Blood cell production (hematopoiesis)

Blood cells are produced in the bone marrow through a process referred to as hematopoiesis. The bone marrow contains hematopoietic stem cells, which are precursors to all blood cells in the body.

Hormone-like proteins called cytokines cause hematopoietic stem cells to proliferate and differentiate through a series of steps into mature red or white blood cells or platelets. Figure 1 provides a simplified diagram of the process of hematopoiesis.

Figure 1. Hematopoiesis



The impact of low blood cell counts

Because blood cells play such important roles in maintaining health, abnormally low numbers of one or more blood cell types can result in a variety of debilitating and dangerous conditions:

- Too few red blood cells (anemia) – Tissues receive insufficient oxygen, causing fatigue, weakness and shortness of breath. Anemia can also exacerbate cardiac problems and damage to other organs; if severe, it can be life-threatening.
- Too few neutrophils (neutropenia) – Increased vulnerability to infection.
- Too few platelets (thrombocytopenia) – Excess bleeding.

MDS CAUSES, RISK FACTORS AND EPIDEMIOLOGY

The exact cause of MDS is unknown in most instances. This is referred to as *de novo*, or primary, MDS. In some patients, environmental risk factors have been identified, including repeated exposure to toxins such as benzenes and some pesticides. In addition, approximately 20 percent of MDS cases develop following chemotherapy or radiation therapy for another disease. This is known as treatment-related, or secondary, MDS.[15]

Although MDS can strike anyone, the majority of the 12,000 to 15,000 new cases in the United States each year occur among people over the age of 60, with a slightly higher incidence in Caucasians and males.[6, 11, 15] Aging is thus the single greatest risk factor for MDS.[6]

The actual incidence of MDS is unknown; however, current estimates are likely conservative. The incidence of MDS appears to be on the rise, most likely due to the growing elderly population and longer overall survival. In addition, greater awareness of MDS, as well as advanced diagnostic capabilities and criteria, have led to improved diagnosis and the identification of more patients with MDS.[6, 15]

PATHOLOGY OF MDS

MDS occurs when myeloid progenitor cells undergo changes that impair their ability to develop into mature, functional blood cells. The defective cells replicate the cellular defect responsible for the disease; thus, all cells produced by the defective cell will carry the same defect.

In addition to being unable to mature into functioning blood cells, defective progenitor cells may have various adverse effects on blood cell development[15]:

- They may produce substances that cause normal progenitor cells to die before they can mature into functional blood cells – a process called apoptosis (programmed cell death).
- They may make too many copies of themselves and "crowd out" healthy cells.

Chromosomal defects

Chromosomal defects occur in approximately 40 to 70 percent of patients with primary MDS and in an even greater percentage of patients with secondary MDS.[18] Chromosomes (Figure 2) contain all of the genetic information that helps to direct normal growth and development of cells, including blood cells; thus, changes in the structure or content of chromosomes can have a profound effect on hematopoiesis.

Cytogenetics (the study of chromosomes) has revealed a number of different types of chromosomal defects in patients with MDS, including:

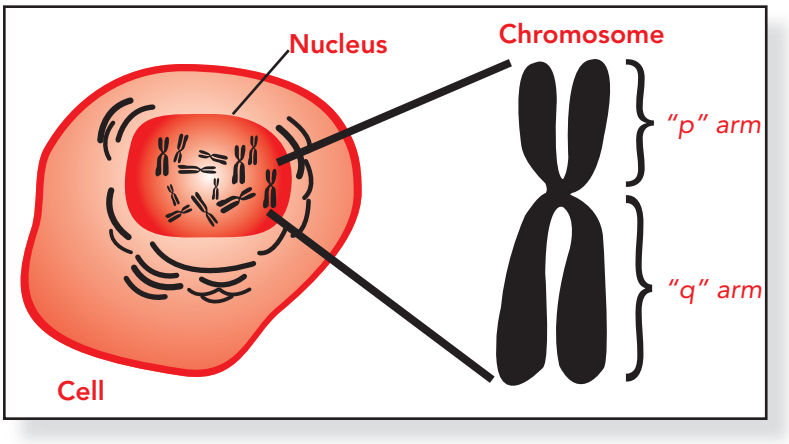
- Missing segments (referred to as deletions); these are the most common defects in MDS[13]
- Duplicate segments
- Segments that have moved (translocated) to other chromosomes

The number and types of chromosomal defects found in MDS can help predict the progression of the illness.[10, 18] Specific defects also define sub-types of MDS (see Classification of MDS).

Chromosomes and cytogenetics – a brief overview

- Human cells contain 23 pairs of chromosomes, labeled 1 through 22, and X and Y. Collectively, they contain an individual's entire set of genes. An individual cell's chromosomal profile is referred to as a karyotype.
- All chromosomes have a short arm and a long arm (see Figure 2). The short arm is designated "p" (for "petit") and the long arm is designated "q".
- Changes in the order and number of genes within a chromosome can have a significant impact on the development of cells and tissues.
- The major types of chromosomal defects include deletions, duplications and translocations.
- When describing chromosomal abnormalities, it is customary to list the chromosome number, the arm that is affected and the type of defect. For example, a deletion in the long arm of chromosome 5 is referred to as "deletion (del) 5q."

Figure 2. Schematic of a chromosome



Other abnormalities

In addition to gross chromosome defects, various abnormalities at the molecular level appear to play a role in MDS. For example, genes that help to suppress the growth of tumor cells (tumor suppressor genes) may be inactivated in some instances.[19] One process for inactivating genes – the addition of methyl molecules to DNA (hypermethylation) – has been associated with the failure of blood cells to develop normally.[20]

CLASSIFICATION OF MDS

As previously stated, MDS is not one, but several disorders that adversely affect the development of one or more types of blood cells. Differentiating the sub-types of MDS from each other is important, since the course, prognosis and treatment for each vary according to type.

Several key characteristics are currently used to classify MDS:

- Morphology, or the appearance of blood cells
- Cytogenetics, or chromosomal defects
- Clinical features

The presence of abnormal types or numbers of cells in the bone marrow and/or blood is a hallmark of MDS and is a fundamental component of classification. Abnormalities may include[21]:

- Increased number of blasts, or cells that have not yet matured into functioning adult blood cells.
- Presence of blasts containing elongated rods called Auer rods.
- Presence of ringed sideroblasts, abnormal red blood cell precursors that are haloed by an iron "ring."
- Various malformations in the nuclei and cytoplasm of red and white blood cell and platelet precursor cells.
- Bone marrow that contains an overabundance of developing blood cells (hyperplastic or hypercellular bone marrow) or too few developing blood cells (hypoplastic or hypocellular bone marrow).

Various combinations of morphological abnormalities and blood cell deficiencies have been recognized as distinct sub-types of MDS, as discussed in more detail in the next section.

MDS classification systems

MDS was first classified into sub-types in 1982 by the French-American-British (FAB) Cooperative Group. This system described five categories of MDS based on morphological differences that had been identified at that time[21]:

- **Refractory anemia (RA)** – Deficiency of at least one blood cell type, most often red blood cells; normal or hypercellular bone marrow with dysplastic changes; no more than 1 percent blasts in the blood and fewer than 5 percent blasts in the bone marrow.
- **Refractory anemia with ringed sideroblasts (RARS)** – Similar to refractory anemia, but with more than 15 percent ringed sideroblasts in the bone marrow.
- **Refractory anemia with excess blasts (RAEB)** – Deficiency of two or more blood cell types; fewer than 5 percent blasts in the blood; 5 to 20 percent blasts in the bone marrow.
- **Refractory anemia with excess blasts in transition (RAEB-T)** – Similar to refractory anemia with excess blasts, but with 5 percent or more blasts in the blood and more than 20 and up to 30 percent blasts in the bone marrow.
- **Chronic myelomonocytic leukemia (CMML)** – Excess monocytes (monocytosis) in the blood; fewer than 5 percent blasts in the blood; 5 to 20 percent blasts in the bone marrow.

In 2001, the World Health Organization (WHO) developed a new classification system to reflect the latest understanding of MDS and incorporate other important features such as chromosome defects. As shown in Table 1, the WHO classification system includes eight different sub-types of MDS.[22]

Table 1. WHO classification of MDS

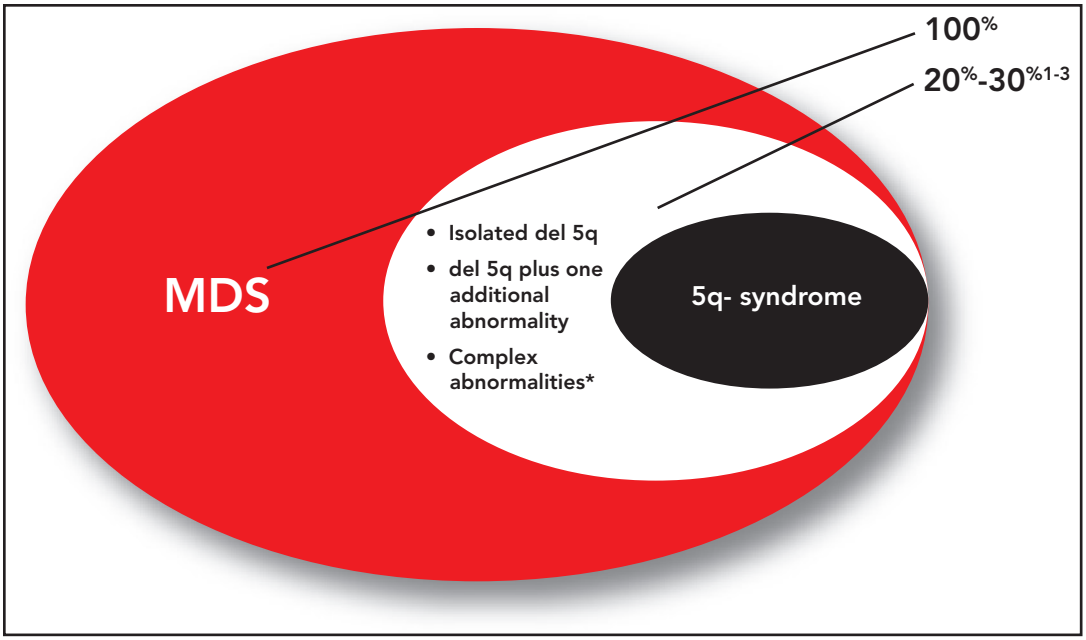
MDS Sub-type	Features
Refractory anemia (RA)	Anemia; fewer than 5% blasts and fewer than 15% ringed sideroblasts in bone marrow
Refractory anemia with ringed sideroblasts	Anemia; at least 15% ringed sideroblasts and fewer than 5% blasts in bone marrow
Refractory cytopenia with dysplasia (RCMD)	Affects two or more blood cell types; fewer than 5% blasts and fewer than 15% ringed sideroblasts in bone marrow
Refractory anemia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Affects two or more blood cell types; at least 15% ringed sideroblasts and fewer than 5% blasts in bone marrow
Refractory anemia with excess blasts – 1 (RAEB-1)	Affects one or more blood cell types; fewer than 5% blasts in blood, 5%–9% blasts in bone marrow
Refractory anemia with excess blasts – 2 (RAEB-2)	Affects one or more blood cell types; 5%–19% blasts in blood, 10%–19% blasts in bone marrow
MDS, unclassified	Affects granulocytes or megakaryocytes; fewer than 5% blasts in bone marrow
MDS with isolated del(5q)	Anemia; platelets normal or increased in blood; fewer than 5% blasts in blood and bone marrow; normal or increased megakaryocytes in marrow; deletion in the long arm of chromosome 5 (del 5q) with no other chromosomal abnormalities

From 22

The 5q minus syndrome

In the WHO system, an isolated deletion in the long arm of chromosome 5 (i.e., without any other chromosomal abnormalities) in combination with specific clinical and morphological findings defines a distinct sub-type of MDS known as 5q minus syndrome.[22] Patients with 5q minus syndrome are a subset of the total population of MDS patients with 5q deletions (see Figure 3). It is important to distinguish 5q minus syndrome from MDS associated with 5q deletions plus other chromosomal abnormalities. As discussed in more detail in Determining Prognosis, the former is associated with a stable clinical course and a good prognosis, while the latter are associated with shorter average survival times and higher rates of progression to AML.[23]

Figure 3. Prevalence of 5q minus syndrome and deletion 5q



**Patients with complex cytogenetics: deletion 5q plus two additional abnormalities.*

SIGNS AND SYMPTOMS OF MDS

Nearly half of patients with MDS have no overt symptoms at the time of diagnosis.[15] Often, a routine blood test reveals low blood cell counts. When symptoms do occur, they differ depending on the type of MDS and the predominant blood cell deficiency (Table 2).

Table 2. Signs and symptoms associated with blood cell deficiencies

Anemia	Neutropenia	Thrombocytopenia
• Fatigue • Shortness of breath • Dizziness • Headaches • Pallor (paleness) • Heart palpitations	• Frequent infections • Infections that do not resolve • Mouth sores • Fevers	• Excessive bleeding (nose bleeds, bleeding while brushing teeth) • Bruising • Petechiae (tiny, rash-like bruises on the skin)

Since numerous diseases are associated with similar symptoms and involve low blood cell counts – for example, vitamin B_{12} deficiency can produce anemia – a diagnosis of MDS cannot be made based on symptoms and abnormal blood tests alone.

DIAGNOSIS

Diagnosis of MDS requires a series of evaluations to rule out other causes of blood cell deficiencies, identify the sub-type of MDS, determine prognosis and define an appropriate treatment plan.[16]

- The first step is to perform a complete blood count (CBC), which reveals a shortage of one or more blood cell types.
- A clinical history identifies signs and symptoms associated with MDS, such as fatigue, shortness of breath and increased infections.
- Examining a blood smear under a microscope, in some patients, may identify abnormal cells that are typical of MDS.
- Microscopic evaluation of bone marrow reveals the extent of blood cell development, the numbers of blasts and the types of dysplastic cells. These data both establish a diagnosis of MDS and help determine the sub-type of disease.
- Cytogenetic examination of bone marrow identifies chromosomal abnormalities that further determine sub-type and prognosis.

DETERMINING PROGNOSIS

Prognosis for patients with MDS varies by sub-type and other factors. The International Prognostic Scoring System (IPSS) for MDS uses variables such as the presence of chromosomal abnormalities and the number and types of blood cell deficiencies to predict survival and the risk of progression to AML (Tables 3 and 4).[10] Despite discrepancies with the WHO classification system, the IPSS is still considered a valuable complement to the WHO system.

Table 3. International Prognostic Scoring System

	Prognostic Score				
Prognostic Variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone marrow blasts (%)	< 5	5–10	–	11–20	21–30
Cytogenetics*	Good	Intermediate	Poor	–	–
Cytopenias	0/1	2/3	–	–	–

* Good = normal, loss of Y chromosome, isolated 5q deletion, 20q deletion
Intermediate = other abnormalities
Poor = 3 or more abnormalities, chromosome 7 abnormalities

Table 4. Survival and risk categorization according to IPSS risk group

	Low	Intermediate-1	Intermediate-2	High
Score	**0**	**0.5–1.0**	**1.5–2**	**≥2.5**
Lifetime development of AML	19%	30%	33%	45%
Median years to AML	9.4	3.3	1.1	0.2
Median survival (years)	5.7	3.5	1.2	0.4

Prognostic scoring is important in determining approaches to treatment and treatment goals. In Low- to Intermediate-1-risk patients, who are likely to have longer survival periods, treatments that provide prolonged improvements in blood cell counts and improve health status are a priority. In the higher-risk categories, more aggressive treatments to extend survival and delay progression to AML are the priority.[16]

The impact of chromosome defects on prognosis

As mentioned previously, the type and number of chromosomal defects present in an MDS patient's blood cells have a strong association with risk of disease progression and survival time. Some chromosome abnormalities are associated with a relatively favorable level of risk, whereas other abnormalities are associated with high risk and a short survival time. Deletion of chromosome 5q, the most common chromosomal defect in *de novo* MDS, provides a good illustration[18]:

- For patients with isolated deletion 5q (i.e., without additional chromosome abnormalities), prognosis is generally favorable, with a nine-year or longer median survival time and a very low rate of AML progression.[23]
- For patients with deletion 5q plus one additional chromosome abnormality, average survival time is less than four years.[23]
- For patients with deletion 5q plus two additional abnormalities, average survival time is less than one year and progression to AML is rapid.[18]

It is important to note that more slowly progressing forms of MDS with longer survival times are still associated with significant burdens to the patient. For example, patients with 5q minus syndrome may experience chronic anemia, compromised quality of life, the need for repeated blood transfusions and the sometimes life-threatening complications of repeated transfusions (see Treatment of MDS).[23]

TREATMENT OF MDS

The majority of patients with MDS die from the complications of blood abnormalities, and up to 30 percent progress to AML.[6, 13] Thus, effective therapy for MDS is critical.

Key objectives for MDS treatment include:

- Improving blood cell deficiencies such as anemia
- Delaying disease progression
- Improving quality of life
- Reducing the number of defective cells in the bone marrow
- Prolonging survival

Current treatment landscape

MDS represents a challenge for clinicians, due to the wide range of sub-types and clinical manifestations. In addition, since most patients with MDS are elderly, coexisting illnesses and an inability to tolerate more intensive therapies often complicate treatment.

Until very recently, MDS treatment focused primarily on temporary relief of the effects of anemia and other blood cell deficiencies – also referred to as supportive therapy. Chemotherapies used to treat some forms of blood cancer have achieved only short, partial remissions in patients with MDS, and treatments that delay or prevent progression to AML have not been identified.[16]

Allogeneic bone marrow transplant (BMT) can result in disease-free survival in up to 40 percent of the selected small numbers of patients that undergo transplantation.[24] However, the inherent risks of BMT and the difficulty finding appropriate donors severely restrict its use, especially in elderly patients.[13]

Over the past few years, however, new approaches to treatment of MDS have emerged. In 2004, the first agent specifically targeted to MDS was approved by the U.S. Food and Drug Administration (FDA), and several promising new therapies are under investigation.[25, 26]

Treatment guidelines for MDS

Various treatment guidelines for MDS have been published. The National Comprehensive Cancer Network (NCCN) published a set of guidelines in 2005 that follows a step-wise progression, starting with supportive care and advancing to investigational therapies or BMT as warranted. Steps are summarized below.[16]

1. Supportive care

The fundamental therapy for all forms of MDS is supportive care, which may vary by sub-type. Ongoing observation and assessment are the foundation of good treatment. Other elements of supportive care are summarized below.

Red blood cell (RBC) transfusions

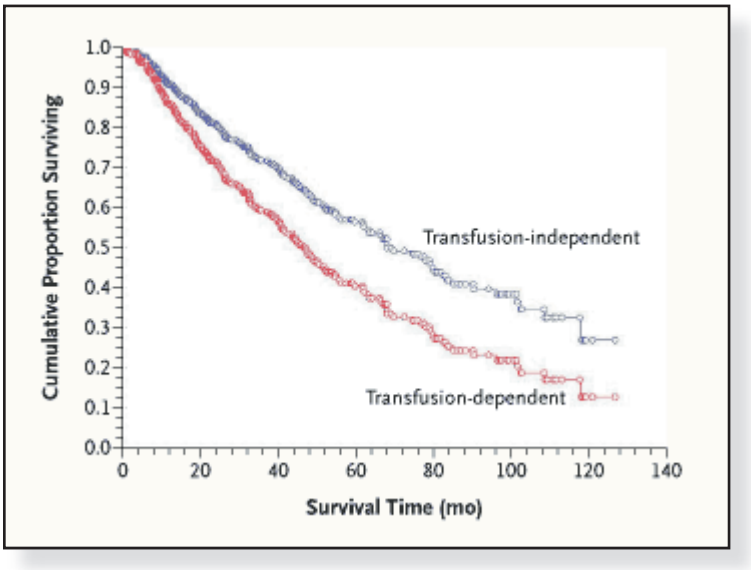
RBC transfusions should be given as needed to correct symptomatic anemia. When patients need repeated transfusions to manage anemia, they are referred to as transfusion dependent.

Iron overload (hemochromatosis) is a potentially deadly consequence of repeated RBC transfusions that requires rigorous management. If untreated, iron overload can cause toxicities to the liver, the heart and other organs (see Iron Overload).

Iron overload is treated with iron chelators, substances that help remove excess iron from the body. The iron chelator most widely used for MDS is administered into a vein, a muscle or under the skin through a continuous pump over a period of 8 to 24 hours.[27] This therapy is associated with several drawbacks including potentially serious side effects in the nervous system, lungs or muscles, as well as the inconvenience of long infusion time.[16, 27] Oral products in development may help overcome some of these limitations.

Patients who are dependent on RBC transfusions have significantly shortened survival times compared with transfusion-independent patients (Figure 4).[9]

Figure 4. Survival time in transfusion-dependent versus transfusion-independent patients with MDS (N=374; p=0.005)



Adapted from New England Journal of Medicine. 2005;352:536-538.

Iron overload

Normally, iron contained in red blood cells is released into the bloodstream when the cells die. In its active state, iron plays a key role in producing energy through a process called oxidation. While this is a vital function, it must be tightly controlled. Unchecked, iron-mediated oxidation can cause damage to body tissues.

In order to keep iron-mediated oxidation under control, the body produces a substance called ferritin that attaches to excess iron and renders it inactive. In this inactive state, iron can be safely stored until it is needed or excreted from the body.

In patients who receive repeated red blood cell transfusions, the extra iron that comes with the extra blood cells can exceed the supply of ferritin. As a result, active iron circulates freely and moves into organs, including the heart and liver. As more active iron builds up in these tissues, it causes increasing damage through oxidation. The most serious consequences of this damage include scarring of the liver and congestive heart failure.[28]

Administration of blood growth factors

The human body produces its own supply of chemical substances that stimulate blood cell production and development. They include:

- Erythropoietin, a hormone that stimulates red blood cell production and maturation.
- Colony stimulating factors (CSF), hormone-like substances that stimulate the production and maturation of blood cells such as neutrophils and monocytes.

The administration of erythropoietin can improve red blood cell counts and reduce the need for RBC transfusions in some patients with MDS.[29] The co-administration of G-CSF with erythropoietin may improve response in some patients who do not respond adequately to erythropoietin alone.[30]

Platelet transfusions

Platelet transfusions are administered to prevent excessive bleeding in patients with low platelet counts. However, platelet transfusions should be delayed for as long as possible and used judiciously, as patients may develop an immune reaction to platelets over time, causing them to "reject" future transfusions.[15]

2. Treatments

Various treatments are recommended for MDS, depending on patient status, disease status and prognostic scores. Highly toxic chemotherapies are reserved for more advanced, severe cases. Allogeneic stem cell transplantation (SCT) is generally reserved for younger patients who are more likely to tolerate the toxicities associated with this procedure.[16]

Low-intensity treatment

One therapy – azacitidine (Vidaza®, Pharmion Corporation) – is indicated for the treatment of all MDS sub-types.[25, 26] This agent inhibits methylation of DNA. As previously mentioned, abnormal methylation of DNA is believed to play a role in aberrant cell proliferation. Azacitidine has been shown to improve white blood cell counts, reduce the need for red blood cell or platelet transfusions and reduce progression to AML in approximately 15 percent of patients. Azacitidine is associated with side effects such as low red cell, white cell and platelet counts, as well as nausea and fatigue.[26]

Other low-intensity treatments are in development.

High-intensity chemotherapy

The NCCN recommends high-intensity chemotherapy for patients with advanced MDS, although with the caveat that these regimens provide inconsistent and less-than-satisfactory response rates. Factors that contribute to poor response rates to high-intensity therapy include[16, 31]:

- Drug resistance
- Older age
- Chromosomal abnormalities

Because high-intensity chemotherapies are associated with serious toxicities, the NCCN recommends their use only in patients who have advanced to the Intermediate-2 prognostic category according to the IPSS (see Determining Prognosis). The NCCN recommends against high-intensity chemotherapies in advanced MDS patients over 60 years of age whose health status is compromised.[16]

Stem cell transplantation

Allogeneic stem cell transplantation (SCT) has been shown to provide prolonged remissions in some MDS patients.[17] This procedure involves transplantation of stem cells from the bone marrow of a healthy donor into a patient with MDS whose own diseased stem cells have been eliminated by intensive chemotherapy and/or radiation as part of the transplant. In MDS, younger age, less advanced disease and a lower percentage of blasts in the marrow are associated with the most favorable outcomes with SCT.[24] Patients with treatment-related MDS tend to have a poorer outcome than those with *de novo* disease.[32]

In addition to the risks associated with intensive chemotherapy and radiation, SCT is associated with graft-versus-host disease, a syndrome in which the transplanted cells recognize the patient as foreign and attack various organs. Thus, the NCCN recommends SCT for patients under the age of 60 whose health status is reasonably good and for whom a suitable donor match can be found.[16]

FUTURE DIRECTIONS

As the previous section makes clear, there is a great need for improved treatments for MDS. There is reason to be hopeful, however. Several promising approaches to treatment are currently under investigation (Table 5), some of which may be available within the coming months. Increasing knowledge about the morphology, cytogenetics and physiology of the various forms of MDS has allowed researchers to identify existing and investigational treatments that may be more active in certain subgroups of MDS patients.

Table 5. Treatments currently under investigation for treatment of MDS

Agent	Proposed mechanism of action
lenalidomide	Not fully understood. Modulates the production of cytokines that inhibit inflammation and promote immune responses; induces the proliferation of T-cells; augments the activity of natural killer cells; inhibits the proliferation of hematopoietic cell lines (cells that reproduce indefinitely under laboratory conditions); and inhibits the growth of new blood vessels
bevacizumab	Inhibits a protein called VEGF, which is considered to play a role in growth of new blood vessels and proliferation of blood cells
arsenic trioxide	Unknown
tipifarnib	Inhibits farnesyl transferase activity
lonafarnib	Inhibits farnesyl transferase activity
decitabine	Inhibits methylation of DNA
imatinib	Inhibits specific receptor kinases
TLK199	Promotes development of granulocytes, which include neutrophils

GLOSSARY OF TERMS

Allogeneic stem cell transplantation – Procedure in which stem cells are removed from the marrow of a healthy, matched donor and transplanted into the recipient patient.

Anemia – Condition in which there are too few red blood cells in the bloodstream, resulting in insufficient oxygen to tissues and organs. Symptoms include fatigue, shortness of breath and weakness; untreated, severe anemia can lead to organ failure and death.

Angiogenesis – Production of new blood vessels. Certain substances in the body induce this process, which is required for normal hematopoiesis.

Apoptosis – Programmed cell death. Within certain tissues, cells reproduce and replenish continuously; apoptosis is necessary to prevent an over-abundance of cells. In many cancers (e.g., leukemia), normal apoptosis is blocked. In MDS, malignant cells release substances that cause an abnormally high rate of apoptosis among blood cell precursors; too many blood cells die before reaching maturity, resulting in a shortage of mature, functioning blood cells.

Auer rods – Elongated rods made up of fused granules that are present in some abnormal blasts in MDS or leukemia.

Basophil – White blood cell in the granulocyte family of leukocytes. In response to inflammation, they release histamines and other substances to destroy invading substances (antigens).

Blast cells – Precursor blood cells that have not yet matured into a functioning state.

Blood cell counts – The number of red and white blood cells and platelets in a person's blood. Blood cell counts are measured with a test referred to as a complete blood count (CBC). The test measures the numbers of red blood cells and all different types of white blood cells and platelets in the blood sample. It also determines the volume occupied by the red blood cells in the blood (hematocrit), the amount of hemoglobin and the number of any immature red and white blood cells that are present in the blood sample.

B-lymphocytes – One of two types of lymphocytes. B-lymphocytes govern humoral immune response by developing antibodies that destroy a specific antigen. The production of memory cells that "remember" a particular antigen allows for a quick response to future invasions by that antigen.

Bone marrow – Soft, spongy tissue located in the center of bones where hematopoiesis takes place. It contains hematopoietic stem cells, which differentiate and mature into red and white blood cells and platelets. Because hematopoietic stem cells have the ability to differentiate into different blood cell types, they are referred to as pluripotent.

Bone marrow aspiration – Extraction of bone marrow tissue through a needle inserted into marrow-rich bone. The sample obtained is used for microscopic examination.

Bone marrow biopsy – Procedure in which a bone marrow sample is removed from the bone. A biopsy is often performed at the same time as a bone marrow aspiration and is especially useful when the aspiration does not yield an adequate bone marrow sample.

Chromosomes – Structures contained in the nuclei of cells that are made up of strands of DNA and the genes encoded within them.

Cytogenetic study – Evaluation of the chromosomal and genetic characteristics of human cells. This determines an individual cell's karyotype.

Cytokine – Hormone-like proteins that govern immune reactions and mediate cell reproduction and function.

Cytopenia – A shortage of one or more types of blood cells.

Cytotoxic – Destructive to cells. Chemotherapies work by being cytotoxic to cancer cells. In most cases, they are cytotoxic to other normal cells as well, which accounts for the serious side effects associated with these agents.

De novo – Disease or process that is new and occurs on its own, rather than being caused by another disease, process or other factors.

Dysplasia – Abnormal cell development.

Dysplastic – Term used to describe cells that develop abnormally.

Enzyme – Protein that acts as a catalyst to induce chemical changes in other substances.

Eosinophils – A white blood cell in the granulocyte family of leukocytes. Eosinophils kill (phagocytize) parasites and mediate allergic reactions.

Erythrocytes – Mature red blood cells.

Erythropoiesis – Process by which red blood cells develop, differentiate and mature in the bone marrow.

Erythropoietin – Naturally occurring hormone that stimulates formation of erythroblasts and release of maturing red blood cells from the bone marrow into the blood.

FAB classification system – Criteria used to classify sub-types of MDS that were developed by a group of French, American and British scientists in 1975. In 2000, the WHO issued a new classification system with revisions based on more recent findings about the morphology and cytogenetics of MDS and its sub-types. Though the WHO system is considered more definitive, some physicians and investigators still use the FAB system to classify MDS.

Farnesyl transferase inhibitors – Novel class of investigational drugs that target a gene mutation referred to as the RAS proto-oncogene, which is expressed in various forms of cancer. It is also believed farnesyl transferase inhibitors act upon other, as yet unidentified pathologic mechanisms.

Ferritin – Substance produced in the body that attaches itself to excess iron in the bloodstream and facilitates its storage in the body.

5q minus syndrome – A sub-type of MDS in which the abnormal blood cells are missing part of the q (long) arm of chromosome number 5 without any other cytogenetic abnormalities. The syndrome is associated with specific clinical and morphological findings, including higher incidence in females; macrocytic anemia; normal or increased numbers of platelets in the blood; fewer than 5% blasts in the blood and bone marrow; and normal or increased numbers of megakaryocytes in the bone marrow, often with nuclear hypolobation.

Genes – Sections of DNA that contain the codes for the production of proteins. These proteins may, for example, determine how a cell in the body will function, including what type of cell it will be, how long it will live and if and how often it will divide.

Graft-versus-host disease – Sometimes fatal immune reaction that may occur in allogeneic transplantation recipients, in which the donor immune system attacks the recipient's tissues. The gastrointestinal tract, liver and skin are most often affected.

Granulocytes – White blood cells that contain enzyme-containing granules in their cytoplasm. They include neutrophils, basophils and eosinophils. The enzymes contained in the granules are released in response to inflammation and have a role in destroying the inflammatory agent (e.g., bacteria, viruses, parasites).

Growth factors – Growth factors stimulate the bone marrow to produce mature blood cells. They are produced naturally in the body; synthetic versions of them have been developed to promote cell production in people with blood cell deficiencies due to disease or as a result of chemotherapy/radiation.

Hematocrit – Measurement of the volume of red blood cells in a blood sample.

Hematopoiesis – Process of blood cell production in the bone marrow. Hematopoiesis begins with hematopoietic stem cells, which differentiate and mature in a series of steps into all types of blood cells.

Hemochromatosis – See iron overload.

Hemoglobin – Iron-protein compound in red blood cells responsible for transporting oxygen from the lungs to the cells.

Hypercellular – See hyperplasia.

Hyperplasia – Increased number of cells. In certain forms of MDS, too many precursor blood cells are present, resulting in hyperplasia. The bone marrow is thus referred to as hyperplastic. Also referred to as hypercellular.

Hypolobation – Containing fewer lobes than usual.

Hypoplasia – Too few cells. In certain forms of MDS, too few precursor blood cells are present. The bone marrow is thus referred to hypoplastic.

Idiopathic – Term used to describe a disease of unknown cause.

Inflammation – Complex process involving proliferation of white blood cells and the release of chemicals in response to tissue injury or invasion of tissue by a foreign substance (referred to as an antigen).

International Prognostic Scoring System (IPSS) – System that assesses prognosis of individual MDS cases according to multiple variables, including the types of blood cells affected, cytogenetics and sub-type of MDS.

Iron chelators – Drugs that bind to active iron in the body tissues that facilitate its elimination in urine.

Iron overload – Condition in which excess iron is stored in body tissues. Excess iron in its active state causes damage to tissues; iron overload is associated with cardiac, liver and glandular disease and, in some cases, can lead to death. Also known as hemochromatosis.

Leukocytes – White blood cells. Among the white blood cells, there are lymphocytes (T-lymphocytes and B-lymphocytes) and myeloid cells (neutrophils, eosinophils, basophils, monocytes and megakaryocytes).

Lineages – Different types (lines) of blood cells in the body. For example, red blood cells represent one lineage; platelets represent another. Depending on the sub-type, MDS may affect only one blood cell lineage (e.g., red blood cells) or multiple blood cell lineages (e.g., neutrophils, platelets, red blood cells).

Lymphocytes – White blood cells that govern the body's immune responses. There are two types – T-lymphocytes and B-lymphocytes.

Macrocytic anemia – Anemia characterized by larger than normal red blood cells (macrocytes) lacking the usual central area of pallor.

Megakaryocyte – Large cell in the bone marrow with a multilobed nucleus from which platelets are produced.

Morphology – The study of cells and cell structure in body tissues.

Myelocytes –Precursor white blood cells that mature and differentiate into granulocytes (neutrophils, eosinophils and basophils).

Neutropenia – Shortage of neutrophils in the bloodstream. In certain forms of MDS, development of mature, adult neutrophils is diminished, and patients are vulnerable to multiple infections that are hard to treat.

Neutrophils – Most common type of white blood cell in human blood. Neutrophils have a pivotal role in helping the body fight infections. Neutrophils engulf invading organisms and release toxins that kill them.

Pancytopenia – Shortage of all types of blood cells.

Petechiae – Small red or purple spots that have a rash-like appearance and are caused by tiny hemorrhages in the skin or mucosa. Petechiae are associated with a shortage of platelets (thrombocytopenia).

Phagocytosis – Process by which white blood cells engulf and destroy microorganisms or invading cells.

Plasma – Straw-colored liquid component of blood.

Platelet – Also called a thrombocyte. A small cell that has an essential role in blood clotting.

Proliferation – Reproduction and increase in number of cells.

Reticulocyte – Mature red blood cell newly released from the bone marrow. Increased numbers of reticulocytes in the bloodstream indicate an increased production of red blood cells.

Stem cells – Hematopoietic stem cells in the bone marrow differentiate and mature into mature, functional red and white blood cells.

Thrombocyte – See platelet.

Thrombocytopenia – Shortage of platelets in the bloodstream associated with an increased risk of bleeding.

T-lymphocyte – One of two types of lymphocytes. T-lymphocytes govern cell-mediated immune response to pathogens or cancerous cells and "alert" B-lymphocytes when an invasive organism is detected. They are also involved in rejection of transplanted organs or tissues.

Vascular-endothelial growth factor (VEGF) – Naturally-occurring substance that promotes production of new blood vessels and reproduction of stem cells.

WHO classification system – System that classifies sub-types of MDS according to the morphologic and cytogenetic features and the numbers and types of blood cells affected. The WHO classification system recognizes eight different sub-types of MDS based on these criteria.

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APPENDIX: RESOURCES

Patient and professional education and information

American Cancer Society (www.cancer.gov)

American Society of Hematology (www.ashonline.org)

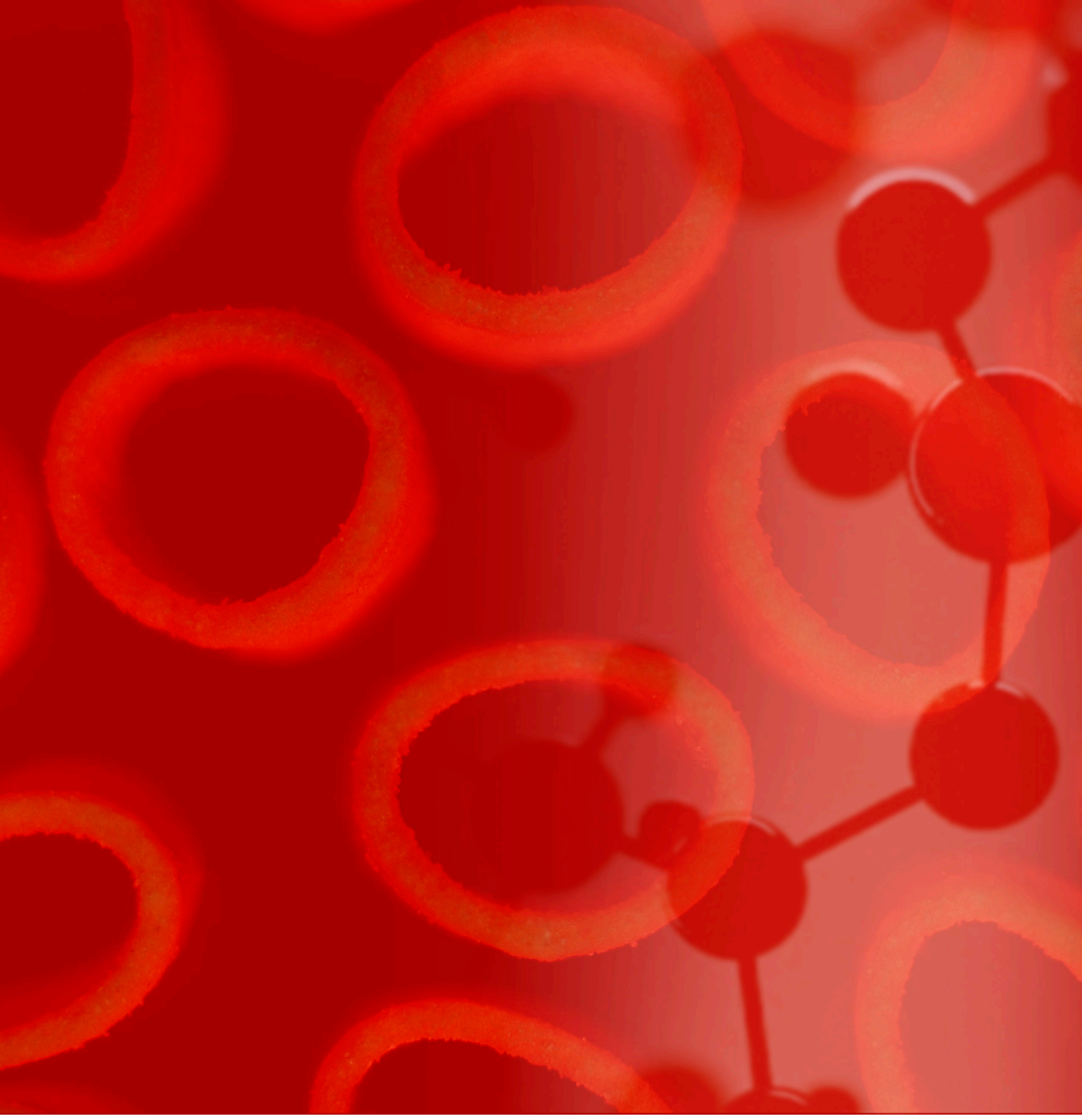
Aplastic Anemia Foundation of America, Inc. (www.aplastic.org)

Aplastic Anemia & MDS International Foundation, Inc. (www.aamds.org)

Leukemia and Lymphoma Society (www.leukemia-lymphoma.org)

Myelodysplastic Syndromes Foundation (www.mds-foundation.org)

National Cancer Institute (www.nci.nih.gov)



 10/05 CELG05182