Building Blocks of Hope

Strategies for Patients & Caregivers
LIVING with MDS

by Sandra Kurtin

A global MDS Foundation print and online patient advocacy initiative, providing a personalized educational program for the patient and caregiver to prepare, participate, and LIVE with MDS.

Book 2
SEEKING TREATMENT
You or someone you know has been diagnosed with MDS. Hearing the words Myelodysplastic Syndrome or MDS can be frightening. The diagnosis of MDS is often unexpected and filled with both immediate and long-term challenges. You probably have many questions. We are pleased that you have requested a copy of the Building Blocks of Hope booklet. It is designed to help get you the information that you are looking for and take an active part in your MDS journey.

There are individual booklets included in the Building Blocks of Hope:

- **Book 1—Understanding MDS**: A complete description of the disease process of MDS and answers to common questions.
- **Book 2—Seeking Treatment**: The treatment of MDS can vary based on the type of MDS you have and how severe it is. This section will provide details about the various approaches to treatment.
- **Book 3—Quick Tips**: The quick tips offered in this section include guidelines for monitoring and managing your symptoms.
- **Book 4—Iron Overload**: Iron overload is a possible outcome of receiving repeated red blood cell transfusions. This section answers common questions, including how iron overload can be treated.
- **Book 5—My MDS Plan**: Understanding the diagnosis of MDS will help you and your caregiver take an active part in your individual treatment plan. My MDS plan provides several tools to allow you to track and manage your journey. You may want to make extra copies of some of these tools before writing on them so that you can continue to track your progress.
- **Book 6—The MDS Foundation**: The MDS Foundation is an international publicly supported organization dedicated to serving the MDS patient, their caregivers, and the professionals that are working to improve the lives of patients living with MDS. The MDS Foundation provides a number of resources which support the Building Blocks of Hope program.

There are several components to the Building Blocks of Hope program. You have received the printed version. These printed materials, along with digital materials, videos, brief educational slides sets, links to online resources, and a number of very practical tools, can be accessed online on the MDS Foundation website [www.mds-foundation.org](http://www.mds-foundation.org). You can also view the complete handbook in a beautiful page-turning format at [http://buildingblocksofhope.com](http://buildingblocksofhope.com). This includes a search feature and thumbnail views that will help you quickly find the information that you are looking for, and is a great way to share information with others. This is a continuously updated document. You can visit the MDS Foundation website or contact the MDS Foundation directly to learn more and check for any new information (see contact information below).

Allow yourself time to adjust to the diagnosis of MDS. Take time to explore the Building Blocks of Hope. We wish you the best in your journey, and hope that the Building Blocks of Hope program will provide you and your caregivers with tools and strategies for LIVING with MDS.

**The MDS Foundation**

1-800-MDS-0839 *(within US only)*  
1-609-298-1035 *(outside US)*  
1-609-298-0590 fax  
website: [www.mds-foundation.org](http://www.mds-foundation.org)  
email: patientliaison@mds-foundation.org
The goals of treatment for MDS are based on the specific type of MDS you have, how the disease is affecting you, and what treatments are available to you. There can be great variability in the way MDS is managed. Treatment for MDS can be grouped into three primary types: Observation, Supportive Care, and Disease Modifying Treatment. Bone Marrow Transplantation and Clinical Trials Participation may be options for you. It is important to understand the treatment recommendations suggested by your oncology provider, how they may affect you on a day-to-day basis, and what the goals of treatment are so that you can ask questions and make an informed choice.
# SEEKING TREATMENT

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparing for the Initial Visit</td>
<td>3</td>
</tr>
<tr>
<td>General Principles of Treatment of MDS</td>
<td>4</td>
</tr>
<tr>
<td>Red Blood Cell Transfusion</td>
<td>7</td>
</tr>
<tr>
<td>Platelet Transfusion</td>
<td>9</td>
</tr>
<tr>
<td>Growth Factors</td>
<td>11</td>
</tr>
<tr>
<td>Disease Modifying Agents</td>
<td>13</td>
</tr>
<tr>
<td>What Is Palliative Care?</td>
<td>16</td>
</tr>
<tr>
<td>Bone Marrow Transplant</td>
<td>17</td>
</tr>
<tr>
<td>The Bone Marrow Transplant Process</td>
<td>18</td>
</tr>
<tr>
<td>Bone Marrow Transplant Evaluation</td>
<td>19</td>
</tr>
<tr>
<td>What Are Clinical Trials</td>
<td>20</td>
</tr>
<tr>
<td>Participating in a Clinical Trial</td>
<td>21</td>
</tr>
<tr>
<td>Clinical Trials in MDS</td>
<td>23</td>
</tr>
<tr>
<td>MDS in Children</td>
<td>24</td>
</tr>
<tr>
<td>Pediatric Information Resources—MDS and Childhood Cancers</td>
<td>27</td>
</tr>
</tbody>
</table>
Preparing for the Initial Visit

What will happen after the diagnosis of MDS is made?

Once the diagnosis of MDS has been established, you will meet with your oncology provider to discuss the diagnosis, prognosis, available treatment options, and the treatment recommended for you, if any. The diagnosis of MDS, as with any type of cancer, can create a variety of emotions including fear, uncertainty, anxiety, and sorrow. The amount and complexity of information that you receive during the diagnostic process and following the diagnosis of MDS can be overwhelming. There are a number of strategies to help you organize your thoughts, your questions, and your concerns so that you can discuss them with your health care providers. Understanding the goals of treatment, how treatment is selected, and what the effects of the treatment might be for you will help you to make decisions about your treatment plan, prepare for the treatment, and plan your daily activities. Being prepared will allow you to ask for help when needed.

Preparing for the initial visit

1. It is helpful to organize any information you have received from the diagnostic procedures you have had so far and bring these with you to your initial visit. Make an extra copy so you do not give your only copy to your provider.
2. Make a list of other health problems, any surgeries and dates, and any family history of cancer or blood disorders.
3. Create a current list of medications including any over-the-counter medications (see: My MDS Plan).
4. Make a list of current providers you might be seeing for other health needs, include the phone and fax numbers to assist with communication between providers (see: My MDS Plan).
5. Prepare your questions for your initial visit. Some of the questions you may want to ask your oncology provider include:
   - What type of MDS do I have and what is my prognosis?
   - What treatment do you recommend for my type of MDS and what are the goals of treatment?
   - When do I need to start treatment?
   - How is the treatment given? How often is it given? How long does each treatment take?
   - What would happen if I do not receive treatment?
   - Am I a candidate for a clinical trial?
   - Am I a candidate for a bone marrow transplant?

It is helpful to write your questions down and have a caregiver take notes during the visit so that you can concentrate on what the provider is telling you. Understanding some of the principles of treatment for MDS will help you to prepare for your visit. Ask for copies of your blood counts, bone marrow report, and any other diagnostic information so that you can organize the information to create your own MDS Profile (see: My MDS Plan).

If you have questions about your diagnosis or treatment options, you may wish to contact the MDS Foundation or one of the MDS Foundations Centers of Excellence for more information. (see: About the MDS Foundation).

To be recognized as a Center of Excellence, an institution must have:

- An established university (or equivalent) program
- Recognized morphologic expertise in MDS
- Available cytogenetics and/or molecular genetics
- Ongoing research, including Institutional Review Board–approved clinical trials
- Documentation of peer-reviewed publications in the field

References:
Kurtin, S., et. al. (2012) Clin J Oncol Nurs, 16(3,suppl), 58-64
What type of MDS do I have and what is my prognosis?
The Myelodysplastic Syndromes (MDS) are a group of bone marrow failure disorders with variable onsets; prognoses, treatment options, and risk of developing leukemia (see: What is MDS? How is MDS classified? How Severe is My MDS?).

How is treatment selected?
The type of treatment selected and the goals of treatment for MDS are based on a number of factors including:

- Your individual health profile
- Other illnesses, how well they are controlled
- Current medications
- General health and ability to be independent in the activities of daily living
- Your individual social and emotional profile
- Your personal choice for proceeding with the recommended treatment options
- The availability of a caregiver
- Proximity to the health care setting
- How the individual treatment may affect your quality of life and lifestyle
- Insurance coverage and finances
- The characteristics of your MDS
- The IPSS-R risk category (see: What is my IPSS score?) Low-risk vs. High-risk
- The presence of certain genetic markers: for example the deletion of 5q or the TET2 mutation (see: Cytogenetics and Molecular Testing in MDS)
- Currently available treatment options including clinical trials (these may be based on geographical location)
- Eligibility for a bone marrow transplant

What are the goals of treatment?
The goals of treatment for MDS are based on the specific type of MDS you have, how the disease is affecting you, and what treatments are available for you. It is important to understand the treatment recommendations suggested by your oncology provider, how they may affect you on a day to day basis, and what the goals of treatment are so you can make an informed choice.

The general goals of treatment vary for the type of disease (low risk vs. high risk) and the type of treatment. There can be variation in the way MDS is managed based on the unique needs of each patient. Treatment for MDS can be grouped into three primary types: Observation, Supportive Care, and Disease Modifying Treatment.

Observation
Observation includes continued monitoring of your blood counts and your symptoms. The frequency of visits for a patient under observation will vary based on the individual trends and any changes in the blood counts or symptoms. Observation is generally reserved for patients with low-risk MDS who have not required blood transfusions or who require them very infrequently.
General Principles of Treatment of MDS

Supportive care
Supportive care includes blood transfusions, growth factors, and other treatments aimed at improving symptoms, such as antibiotics for an infection, nutritional support, treatment of transfusion related iron overload, spiritual and emotional support. Supportive care is appropriate for any patient with the diagnosis of MDS. Certain types of supportive care are administered based on specific criteria. The benefits of supportive care are generally temporary as these strategies do not affect the underlying disease.

| Common forms of supportive care aimed at improving blood counts include: |
| Blood transfusion | Packed red blood cells, platelets |
| Red blood cell growth factors | Approved for patients with lower-risk MDS in Europe. |
| White blood cell growth factors | Approved for use in Nordic countries. |

| Common forms of supportive care for transfusion-related iron overload include: |
| Deferasirox (Exjade*) | Approved for iron overload in the United States and Nordic countries. |
| Deferoxamine (Desferal*) | Approved for iron overload in Canada, Europe, Japan, Nordic countries, the United Kingdom, and the United States. |

Disease modifying treatment
The decision to start disease modifying treatment is generally made based on changes in blood counts, changes in symptoms, or the presence of higher-risk disease. These “treatment triggers” include: blood counts getting worse (progressive cytopenias: anemia, thrombocytopenia, or neutropenia), increasing blasts, or increased frequency of blood transfusions. All of these findings suggest the MDS is changing and limiting the normal function of the bone marrow (see: What Happens to the Bone Marrow in MDS). Disease modifying treatments have the ability to change one or more of the abnormal components of the MDS.

| Common disease modifying treatments for MDS |
| Antithymocyte globulin, cyclosporine | Off-label use for low-risk and hypocellular MDS in Canada, Europe, Japan, Nordic countries, and the United States. |
| Azacitidine (Vidaza*) | Approved for treatment of higher-risk MDS in Europe, Nordic countries, and the United States. |
| Decitabine (Dacogen*) | Approved for treatment of IPSS higher-risk or low-risk MDS with thrombocytopenia or neutropenia in the United States. |
| Lenalidomide (Revlimid*) | Approved for treatment of low-risk MDS with del(5q) in the United States and Canada |
General Principles of Treatment of MDS

Low-risk MDS
Low-risk MDS is classified as having a lower IPSS score and favorable genetic features.

<table>
<thead>
<tr>
<th>IPSS</th>
<th>Score</th>
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<tbody>
<tr>
<td>Low Risk</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate-1 Risk</td>
<td>0.5-1.0</td>
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</table>

<table>
<thead>
<tr>
<th>IPSS-R</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>&lt;1.5</td>
</tr>
<tr>
<td>Low</td>
<td>&gt;1.5-3.0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;3.0-4.5</td>
</tr>
</tbody>
</table>

Goals of treatment for low-risk MDS:
1. Improve hematopoiesis (production of the components of blood).
2. Reduce the number of blood transfusions and optimally eliminate the need for transfusions completely (transfusion-independence).
3. Improve quality of life.
4. Extend survival.

High-risk MDS
High-risk MDS is classified as having a higher IPSS or IPSS-R score or selected high-risk features. (see: What is my IPSS score? and How Severe is My MDS?).

<table>
<thead>
<tr>
<th>IPSS</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate-2 Risk</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>High Risk</td>
<td>&gt;2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IPSS-R</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>4.5-6.0</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;6.0</td>
</tr>
</tbody>
</table>

Goals of Treatment for high-risk MDS:
1. Delay time to leukemic transformation.
2. Improve quality of life by improving symptoms and treatment burden.
3. Improve survival.

References:
Red Blood Cell Transfusion

Red blood cell transfusions are defined as the intravenous (IV, through a vein) infusion of red blood cells. Whole blood is collected from donors and then separated into various blood components. Red blood cells (RBCs) or packed red blood cells (PRBCs) are one component of whole blood.

Why are red blood cells given?
Red blood cell transfusions are a common way to provide temporary relief of the symptoms of anemia associated with MDS. Nearly 90% of patients with MDS are treated with red blood cell transfusions at some point during their diagnosis with MDS.

How are red blood cells administered?
Red blood cells are administered through an intravenous (IV) catheter in the arm, a peripherally inserted central catheter in the upper arm (PICC line) or an implanted central catheter in the chest (port-a-cath or Hickman catheter).

How do I know if I need a blood transfusion?
Most patients with MDS will have regular blood tests to monitor their disease. Your provider will notify you if your hemoglobin is at a level that may require a PRBC transfusion. The decision to transfuse PRBCs will be based on your symptoms as well as your blood counts. You may also notice symptoms of anemia such as increasing fatigue, a pale complexion, shortness of breath with exertion, or a faster heart rate. These symptoms should be reported to your health care team (see: Quick Tips: Anemia).

What is the process for receiving a red blood cell transfusion?
Once the decision is made to transfuse, you will need a laboratory test (blood sample) to “crossmatch” your blood to available units of blood in your nearest blood bank. This test is necessary to ensure the transfused donor cells are compatible with your blood cells. This is also how your blood type and whether you have any antibodies in your blood are determined. The blood sample will be sent to the blood bank in your area for testing. The blood bank will then search the available donor units for blood that matches your blood type and any antibodies you may have. This can take a few hours to several days depending on blood availability and your individual blood profile.

You will have a wrist band (usually red) placed on your wrist when the sample is taken. This should not be removed until after you have received the transfusion. The blood identification band will be used to verify the blood match prior to you receiving the transfusion.

What can I expect on the day that I receive the transfusion?
The process for obtaining matched red blood cells and infusing them may require more than one day. Each facility has its own policy for the rate of red blood cell transfusion. Most often, 2 units of PRBCs are administered based on the patient’s symptoms and hemoglobin level. Each unit of red blood cells is administered over 2–4 hours and should never take longer than 4 hours because of the risk of bacterial growth in the blood product. You will need to have an IV catheter placed for the transfusion unless you have an existing intravenous access device. The transfusion of 2 units of PRBCs may take anywhere from 4–5 hours once the blood is obtained.
How often will I receive red blood cell transfusion?

How frequently transfusions need to be administered will vary depending upon the severity of symptoms and the hematocrit or hemoglobin level. Transfusion intervals (the time between one transfusion and the next) may vary from every few months in lower risk MDS to every 2 to 6 weeks in higher risk disease. In some MDS patients, the transfusion interval may be as often as once every 1 to 2 weeks. MDS patients who require a series of transfusions of red blood cells are considered to be transfusion-dependent. Transfusion-dependence is a common trigger to consider disease modifying treatment (treatment directed at the abnormalities in the bone marrow) to improve production of normal blood cells, including red blood cells and limit continued exposure to excess iron (iron overload).

What are the risks associated with red blood cell transfusion?

There are some potential risks associated with red blood cell transfusion. Most side effects are mild and are easily managed with medications. More serious reactions can happen, but are rare. The side effects can be divided into two time frames: short-term risks and long-term risks.

Short-term risks

- Fever, rash, itching, and/or hives are common side effects that you may experience and usually are mild.
- A severe allergic reaction may occur, but is rare.
- Difficulty breathing is uncommon, but can happen with severe allergic reactions or a build-up of fluid in your lungs.
- Nurses will be monitoring you throughout your transfusion to identify any reactions early.

Long-term risks

Transmission of an infection (such as HIV or hepatitis) through a blood transfusion is very low. Although blood products are tested for diseases, it will never be possible to guarantee that a transfusion will not transmit an infection. After many transfusions of blood, you may develop antibodies to donor blood which will make it more difficult for the blood bank to “match” your blood. Iron overload may occur if you have received 10-20 units of blood.

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, and 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.

References:
A platelet transfusion is defined as the intravenous (IV, through a vein) infusion of platelets. Whole blood is collected from donors and then separated into various blood components. Platelets are one component of whole blood.

**Why are platelets given?**
Platelet transfusions are a common way to provide temporary relief of the symptoms of thrombocytopenia associated with MDS or its treatment. They are most often given when the risk of bleeding is increased. Platelet transfusions are given much less frequently than red blood cell transfusions in patients with MDS.

**How are platelets administered?**
Platelets are administered through an intravenous (IV) catheter in the arm, a peripherally inserted central catheter in the upper arm (PICC line) or an implanted central catheter in the chest (port-a-cath or Hickman catheter).

**How do I know if I need a platelet transfusion?**
Most patients with MDS will have regular blood tests to monitor their disease. Your provider will notify you if your platelet count is at a level that may require a platelet transfusion. You may also notice symptoms of thrombocytopenia (low platelets) such as increased bruising, petechiae, or episodes of bleeding. These symptoms should be reported to your health care team (see: *Quick Tips: Thrombocytopenia*). The decision to transfuse platelets will be based on your symptoms as well as your blood counts.

**What is the process for receiving a platelet transfusion?**
Once the decision is made to transfuse, you will need a laboratory test (blood sample) to “crossmatch” your blood to available units of platelets in your nearest blood bank. This can take a few hours to several days depending on blood availability and your individual blood profile.

You will have a wrist band placed on your wrist when the sample is taken. This should not be removed until after you have received the transfusion. The blood identification band will be used to verify the blood match prior to you receiving the transfusion.
Platelet Transfusion

What can I expect on the day that I receive the transfusion?
The process for obtaining platelets and infusing them may require more than one day. Each facility has its own policy for the transfusion of platelets. Platelets may be either random donor units (the platelet component from multiple units of whole blood) or single donor units (individual donors donate a single unit of platelets). Most often, 1 unit of single donor platelets or 4-6 units of random donor platelets are administered based on the patient’s symptoms and platelet count. Platelets are infused over 15-30 minutes depending on the volume of each unit. You will need to have an IV catheter placed for the transfusion unless you have an existing intravenous access device. Transfused platelets do not last long (hours to a couple days). The frequency of transfusions will be determined on how well your bone marrow is able to produce platelets, your symptoms and your platelet count.

What are the risks associated with platelet transfusion?
There are some potential risks associated with platelet transfusion. Most side effects are mild and are easily managed with medications. More serious reactions can happen, but are rare.

Short-term risks
- Fever, rash, itching, and/or hives are common side effects you may experience and usually are mild.
- A severe allergic reaction may occur, but is rare.
- Difficulty breathing is uncommon, but can happen with severe allergic reactions.
- Nurses will be monitoring you throughout your transfusion to identify any reactions early.

Long-term risks
- The development of antibodies would make it more difficult to find suitable donor units.
- Transmission of an infection (such as HIV or hepatitis) through a platelet transfusion is very low.

References:
Growth Factors

Growth factors are synthetically produced proteins that mimic the normal proteins needed for hematopoiesis (normal development of blood cells). There are growth factors that stimulate the production of red blood cells, granulocytes (a type of white blood cell) and platelets. These growth factors are considered a form of supportive care.

Red blood cell growth factors (Erythropoietin stimulating agents or ESAs)
Red blood cell growth factors may improve anemia by improving red blood cell production. Red blood cell growth factors contain the protein erythropoietin. Erythropoietin (EPO) is a natural hormone produced by the kidneys to help red blood cells develop fully so that they can carry oxygen. The level of erythropoietin in the blood can be measured. Patients with a serum erythropoietin level <500 IU/L who require fewer than two units of packed red blood cells (PRBCs) every 4 weeks have been shown to benefit most from the administration of synthetic erythropoietin stimulating proteins.

Available agents:
- **Erythropoietin (EPO) (Procrit®)** is a synthetic form of EPO. It is administered as a subcutaneous (under the skin) injection once weekly in low-risk MDS patients to improve red cell production. Doses are based on individual response and regional guidelines for use.
- **Darbepoetin (Aranesp®)** is a longer acting synthetic form of EPO. It is administered as subcutaneous injection (under the skin) every 2-3 weeks in low-risk MDS patients to improve red cell production. Doses are based on individual response and regional guidelines for use.

ESAs in the United States must be administered under the APPRISE safety program known as a REMS program.

White blood cell growth factors
MDS patients often have cytopenias resulting in low neutrophil counts and an increased risk of infection. White blood cell growth factors are synthetic proteins used to stimulate the bone marrow to produce more neutrophils to fight infection in patients with bone marrow diseases or undergoing chemotherapy.

Available agents:
- **Filgrastim (Neupogen®)** Short acting synthetic form of granulocyte colony-stimulating factor (GCSF).
- **Pegfilgrastim (Neulasta®)** PEGylated (long-acting) synthetic form of GCSF.
- **Sagramostim (Leukine®)** Recombinant granulocyte macrophage colony-stimulating factor functions to increase white cell production.

Platelet growth factors
Platelet growth factors are agents used to promote platelet production (thrombopoiesis) to prevent thrombocytopenia and bleeding. These agents are not currently approved for use in MDS.

Available agents: *(currently not approved for use in MDS)*
- **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.
Growth Factors

Oprelvekin (Neumega®), 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 orelvekin 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®) 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 marrow 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.

References:
Disease Modifying Agents

Disease Modifying Agents are treatment with the potential to affect the underlying abnormalities that cause MDS. They have the potential to change the natural history of the disease and extend survival. The decision to start treatment with a disease modifying agents is based on common treatment triggers such as transfusion dependence, increasing blasts, higher risk MDS, and progressive or symptomatic cytopenias.

**FDA Approved Agents for Treatment of Myelodysplastic Syndromes**

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<thead>
<tr>
<th></th>
<th>Azacitidine</th>
<th>Decitabine</th>
<th>Lenalidomide</th>
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<tr>
<td><strong>Indication</strong></td>
<td>All 5 FAB subtypes (RAa, RARSa, RAEB, CMML, RAEB-t)</td>
<td>Int-1/Int-2/high risk per IPSS, as well as MDS</td>
<td>Transfusion-dependent MDS low-int-1 MDS with del(5q) with or without additional chromosomal abnormalities</td>
</tr>
<tr>
<td><strong>Drug class</strong></td>
<td>Hypomethylating agent</td>
<td>Hypomethylating agent</td>
<td>Immunomodulatory agent (IMiD)</td>
</tr>
<tr>
<td><strong>Key clinical trials</strong></td>
<td>CALGB 9221, phase I/II &lt;br&gt; CALGB 8421 phase II continuation (2000) &lt;br&gt; Established efficacy and safety &lt;br&gt; AZA-001, phase III international, multicenter &lt;br&gt; Int-2, high-risk MDS &lt;br&gt; First survival data for active therapies in MDS</td>
<td>D-0007, phase I/II (2003) &lt;br&gt; Established efficacy and safety &lt;br&gt; ADOPT trial (2007) phase III randomized, multicenter trial &lt;br&gt; Established new dosing guidelines &lt;br&gt; Decitabine 20 mg/m² IV given over 1 h days 1–5 &lt;br&gt; Outpatient treatment feasible</td>
<td>MDS-001, phase I/II (2002) &lt;br&gt; Established efficacy and safety &lt;br&gt; MDS-003, phase II multicenter trial, lenalidomide in del(5q) led to FDA approval based on efficacy and safety &lt;br&gt; MDS-002, phase II multicenter trial, lenalidomide in non-del(5q) low–Int-1 MDS. Confirmed activity in non-(del)5q MDS; confirmed safety and efficacy</td>
</tr>
<tr>
<td><strong>Primary end points met (IWG)</strong></td>
<td>Improved overall survival &lt;br&gt; Hematologic improvement &lt;br&gt; Transfusion independence &lt;br&gt; Cytogenetic response &lt;br&gt; Safety and efficacy</td>
<td>Hematologic improvement &lt;br&gt; Transfusion independence &lt;br&gt; Cytogenetic response &lt;br&gt; Safety and efficacy</td>
<td>Hematologic improvement &lt;br&gt; Transfusion independence &lt;br&gt; Cytogenetic response &lt;br&gt; Safety and efficacy</td>
</tr>
<tr>
<td><strong>Common side effects</strong></td>
<td>Myelosuppression is most common &lt;br&gt; Injection site reactions &lt;br&gt; Nausea and vomiting &lt;br&gt; Constipation &lt;br&gt; Contraindicated in patients with hepatic tumors &lt;br&gt; Use with caution in renal impairment &lt;br&gt; May cause fetal harm</td>
<td>Myelosuppression is most common &lt;br&gt; Nausea and vomiting &lt;br&gt; Constipation &lt;br&gt; Hyperbilirubinemia &lt;br&gt; Use with caution in renal impairment &lt;br&gt; May cause fetal harm</td>
<td>Myelosuppression is most common &lt;br&gt; Rash &lt;br&gt; Diarrhea &lt;br&gt; Requires renal dose adjustment &lt;br&gt; Nonteratogenic in animal studies &lt;br&gt; Analog of thalidomide &lt;br&gt; Must be prescribed through Revassit program for safety &lt;br&gt; May cause fetal harm</td>
</tr>
<tr>
<td><strong>Mode of use</strong></td>
<td>SC or IV x 7 days &lt;br&gt; Every 28 days &lt;br&gt; Outpatient regimen &lt;br&gt; Treat until unacceptable toxicity or disease progression</td>
<td>IV daily for 5 days over 1 hour &lt;br&gt; Every 28 days &lt;br&gt; Outpatient regimen &lt;br&gt; Treat until unacceptable toxicity or disease progression</td>
<td>10 mg orally days 1–21 &lt;br&gt; Every 28 days &lt;br&gt; Treat until unacceptable toxicity of disease progression</td>
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Disease Modifying Agents

Hypomethylating agents

Hypermethylation, the accumulation of compounds called methyl groups on portions of DNA, has been identified as one of the contributing factors in the development of MDS and leukemia. These compounds silence or turn off genes that are necessary for the normal development and maturation of blood cells. Hypermethylation is a constant process. Hypomethylating agents, drugs that block the methyl compounds, have been shown to improve normal blood cell development (hematopoiesis) in patients with MDS by allowing the silenced genes to be turned back on. There are currently two hypomethylating agents available: 5-azacytidine (azacitidine) and 5-aza-2-deoxycytidine (decitabine).

Azacitidine (Vidaza®) www.vidaza.com

Azacitidine was the first drug approved by the FDA specifically to treat MDS. It is administered by subcutaneous (under the skin) or by intravenous injection. The intravenous and subcutaneous dosing schedules are the same. Several clinical trials showed that, compared with patients who did not receive azacitidine, MDS patients treated with one subcutaneous injection of azacitidine 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 azacitidine. In some clinical trials, the time to onset of AML was significantly delayed in azacitadine-treated patients when compared with patients who did not receive azacitidine. Results of a large phase III study in 328 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 azacitadine significantly prolonged overall survival (24.4 months versus 15 months). More convenient dosing schedules (5-day subcutaneous schedules) and a short intravenous infusion for azacitadine have also been investigated. The most common side effects seen with azacitadine are myelosuppression, nausea, constipation, and injection site reactions. An oral formulation has been developed and is currently in clinical trials.

Decitabine (Dacogen®) www.dacogen.com

Decitabine, (also called 5-deoxyazacytidine), is a DNA hypomethylating agent like azacitidine and works like azacitadine. In other words, decitabine reduces DNA methylation, and restores the normal functioning of tumor suppressor genes in MDS. 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. The most common side effects seen with decitabine are myelosuppression, nausea, and constipation.

Immunomodulatory agents www.revlimid.com

Immunomodulatory agents are a form of disease modifying treatment targeted at the bone marrow microenvironment and elements of the abnormal MDS cells (malignant clone). 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. 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 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).

**Immunosuppressive agents**

Immunosuppressive agents, although not currently FDA approved for the treatment of MDS, may be used in patients with low-risk MDS or hypocellular MDS in the clinical trial setting or in selected clinical settings.

**Cyclosporine**: Used primarily to inhibit immune rejection. In low doses, it can be used for the treatment of hypocellular MDS and MDS with refractory anemia (RA).

**Antithymocyte Globulin (ATG)**: A T cell depleting agent that exists in two forms: rabbit or equine. It is used in selected cases of MDS but must be administered in the inpatient setting with close surveillance for anaphylaxis reaction.

**Alemtuzumab (Campath)**: An antibody to the CD52 receptor found on many mature immune cells, including T and B cells, is being used primarily in the clinical trials setting.

**Induction chemotherapy**

A patient with higher-risk MDS has a higher probability of disease progression to AML. For this reason, your physician 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. 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, mouth sores, nausea, vomiting, diarrhea and infections. There are a number of different chemotherapy drugs and combinations of drugs that may be used. All of these regimens affect normal cells of the body in addition to the MDS cells. For this reason, this type of treatment generally requires hospitalization for days to weeks depending on how well it is tolerated and how quickly the bone marrow and other cells in the body recover. Aggressive supportive care including transfusions, intravenous fluids, antibiotics, nutritional support, pain management, and psychosocial support are necessary during the hospitalization.

Once there is evidence of bone marrow recovery (improved counts) and improvement of any side effects of treatment, you will be discharged to be followed up in the outpatient setting. A bone marrow biopsy and aspirate will be repeated either while hospitalized or after discharge to evaluate the effectiveness of the treatment. 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.
What is palliative care for MDS?
Myelodysplastic Syndromes (MDS) can affect the body, the mind, and the spirit. Patients with MDS, their caregivers, and families may have trouble in one or more of these areas during any stage of the illness. Palliative care for patients with MDS can be started as soon as they are diagnosed with the disease. The majority of oncology health care professionals will incorporate the elements of palliative care into your day-to-day care. Palliative care offer assistance with:

- Difficult treatment decisions
- Physical symptoms: for example pain, nausea and vomiting, diarrhea, constipation, fatigue, nutritional needs, etc.
- Emotional needs such as depression or anxiety
- Social needs
- Financial direction
- Spiritual support

The palliative care team
The palliative care team will work with the patient and their caregivers to identify his or her needs, goals and fears. Palliative medicine utilizes a multidisciplinary approach to patient care, relying on input from physicians, pharmacists, nurses, chaplains, social workers, psychologists, and other allied health professionals in formulating a plan of care to relieve suffering in all areas of a patient’s life. This multidisciplinary approach allows the palliative care team to address physical, emotional, spiritual, and social concerns that arise with advanced illness or incurable diseases. Some cancer centers or clinics have designated palliative care teams; other centers may have access to trained individuals upon request. A palliative care team may include one or more of the following:

- Physician(s)
- Nurse practitioners (NP) or physician assistants (PA)
- Oncology nurse specialist
- Social worker
- Pain service
- Chaplain service or other spiritual support services
- Nutritionist
- Physical therapist
- Financial counselor

Patients with lung cancer who received palliative care starting in the early stages of the illness had a better quality of life, less depression, and lived longer than those that did not receive palliative care. Though more research with MDS patients is needed, this study suggests that palliative care starting in the early stages of disease, such as MDS, may benefit patients. Although palliative care is not intended as a cure for MDS, it may increase the chances of survival by preparing the patient for the road ahead and supporting them and their families.

References:
ASH Education Book January 1, 2008 vol. 2008 no. 1 465
Termel, J.S., et. al. (2010). Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer. NEJM 363:8 nejm.org august 19, 2010
What is a bone marrow transplant?
A bone marrow transplant (BMT), also known as a stem cell transplant or hematopoietic stem cell transplant (HSCT) involves treatment with high dose chemotherapy and possibly radiation followed by the infusion of stem cells (progenitor cells). These stem cells have the capacity to restore bone marrow function (see: What does bone marrow do?). There are significant risks with this procedure. Therefore, although blood or marrow transplantation offers a potential cure for MDS, this procedure is available to only a small proportion of adult MDS patients.

Bone marrow transplant
Allogeneic bone marrow transplantation offers the only currently available treatment option with the potential to completely remove the malignant MDS clone (MDS factory cells) from the bone marrow. Removal of the MDS clone is necessary to “cure” MDS. As the only proven cure for MDS, allogeneic hematopoietic stem cell transplantation (HSCT) should be considered for transplantation-eligible patients with high-risk disease (see: Am I a candidate for a bone marrow transplant?). Allogeneic bone marrow transplants represent the most aggressive treatment option and are not suitable for most patients with MDS.

There are different types of transplants: autologous and allogeneic. Autologous stem cells are obtained from the patient and used for the same patient’s transplant. Allogeneic stem cells are obtained from another individual who is genetically as similar to the patient as possible. This is usually a brother or a sister, but may be an unrelated volunteer donor. For MDS, allogeneic stem cell transplant is most common.

The allogeneic stem cells are usually obtained from the blood stream of the donor after the donor receives a medication to stimulate production of stem cells. We call these mobilized peripheral blood stem cells. On rare occasion, we collect cells from the bone marrow of the donor, called bone marrow stem cells.

You will be human leukocyte antigen (HLA) typed to determine your profile. This is a simple blood test but it is the most critical component of finding a perfect “match” for your transplant. HLA antigens are proteins or markers found on the surface of most cells in your body. Your immune system uses these markers to recognize which cells belong in your body and which do not. Human leukocyte antigen (HLA) typing is used to match patients and donors for stem cell and bone marrow transplants.

Am I a candidate for a bone marrow transplant?
The first step toward a bone marrow transplant is to determine if you are a candidate for this type of treatment. Your provider and health care team will evaluate several factors known as eligibility criteria. The most common eligibility criteria include:

• Age less than 65 years (some exception may be made at some centers)
• Availability of a HLA identical matched donor
• Good heart, lung, liver, and kidney function
• Physically active and able to perform daily activities independently

There are many resources available to help you understand blood and bone marrow transplantation for MDS.

• National Marrow Donor Program (NMDP) www.marrow.org
• Blood and Marrow Transplantation Information Network www.bmtinfonet.org
• National Coalitions for Cancer Survivorship www.canceradvocacy.org/toolbox
• Be The Match www.marrow.org
Blood or bone marrow transplantation is a complex multi-step process. It is important for you and your caregiver(s) to familiarize yourselves with each step in the process. This will help you in planning your time, resources, and areas where you may need assistance.

1. **Pre-transplant treatment** — It is always best if your MDS is well-controlled prior to proceeding to transplant. This will require disease modifying therapy.

2. **Transplant evaluation** — (see: Bone Marrow Transplant Evaluation)

3. **Donor search** — During your transplant evaluation, you will be asked about possible sibling donors. If there are no sibling matches, a donor search will be initiated. This may take days to months; and, in some cases, a suitable donor cannot be located. The best donor will match all of your DNA markers. In some cases, donors who match most, but not all, of the DNA markers will be considered. This type of transplant (mismatched) carries greater risks.

4. **Pre-admission consent signing** — After a donor has been located, you will return to the transplant center with your designated caregiver(s) for a pre-hospitalization visit. This visit usually takes more than 1 hour and will include a detailed discussion of the possible risks and benefits of the transplant for you. It is important to prepare any questions that you or your caregivers may have prior to this visit. If you wish to proceed with the transplant, you will sign a consent form prior to being hospitalized for the transplant.

5. **Conditioning regimen** — Prior to proceeding with the transplant, you will need to have high-dose chemotherapy to remove the remaining elements of your bone marrow which carry the MDS clone. This will make room for the new stem cells from your donor that will repopulate your bone marrow with new factory cells (progenitor or stem cell). This treatment phase requires hospitalization at the bone marrow transplant center for several weeks.

6. **Stem cell infusion** — The day of infusion, or transplant, is commonly referred to as “Day 0.” The donor stem cells are infused via central venous access. The actual infusion can take as long as an hour depending on the number of frozen bags of HSC product. There may be other activities as part of the infusion, such as hydration, that will result in a day-long procedure.

7. **Engraftment** — Blood count recovery, or “engraftment,” will be the first sign that the transplanted stem cells have populated your bone marrow and are starting to produce the elements of blood. Engraftment is established when absolute neutrophils are >500 cells/dL for three consecutive days or >1,000 for one day, and platelets remain >20,000 independent of transfusion for at least 7 days.

8. **Transplant side effect management** — Allogeneic stem cell transplants are associated with considerable treatment-related side effects, both during and after the transplant. These side effects will be discussed with you and your caregiver(s) at the pre-transplant visit.
Selecting a transplant center

Once you and your health care team have determined a blood or bone marrow transplant is a good treatment option for your MDS, there are a number of things for you and your caregiver(s) to consider.

How do I choose a bone marrow transplant center?

There are more than 200 transplant centers in the United States alone. Finding one that best suits your needs may seem like an overwhelming task. The choice of centers may be based on a number of factors:

- The recommendations made by your primary oncologist.
- The transplant centers under contract with your insurance plan.
- The rating of the individual center.
- The proximity of the center to your home.

A directory of blood and bone marrow transplant centers can be found online:

- BMT Information Network  [www.bmtinfonet.org](http://www.bmtinfonet.org)
- The National Marrow Donor Program (NMDP)  [www.marrow.org](http://www.marrow.org)
- The Center for International Blood and Marrow Transplant Research  [www.cibmtr.org](http://www.cibmtr.org)

The bone marrow transplant evaluation

Once you have identified the transplant center, you will be referred for a formal consultation and evaluation. This process may take several days and will include a number of blood tests, radiology examinations, breathing tests, and a bone marrow biopsy and aspirate. You will meet with members of the transplant team including the transplant physician, nurses, social workers, and dieticians. The screening visit is to be certain that a bone marrow transplant is the best treatment option for you.

What questions should I ask my bone marrow transplant physician?

There are a number of questions that you and your caregiver(s) may want to ask when you meet with the members of the transplant team:

1. Is the facility approved by your insurance company for transplant?
2. Is the program accredited by the Foundation for Accreditation of Cellular Therapy (FACT)? (This agency conducts rigorous inspections of transplant programs and certifies a program if it offers high quality care.)
3. What tests will I need before the transplant?
4. Is housing available in the area for post-transplant care and what is the recommended/required duration to reside locally?
5. What is the experience of the transplant team in treating patients with MDS?
6. Is there extra financial support available from the institution for non-insurance costs?
7. What is the usual length of hospital stay during transplant?
8. How often will I need to be seen in the clinic after discharge?
9. Does the transplant program have a long-term follow-up program to help you with medical issues that may come up months or years after transplant?
10. Are there emotional support services for me, my donor, my caregiver and my family?
11. What is the center’s success rate with stem cell transplants?
12. What are the expectations for the caregiver(s)?
What are clinical trials?
Clinical trials offer an option for treatment under the guidance of a research protocol. Clinical trials provide several important benefits:

1. Are an important part of developing new treatments for MDS and other diseases
2. Help to improve diagnostic techniques
3. Identify new targets for treatment
4. May offer treatment options which are not otherwise available
5. Help to refine treatment strategies, such as refinement of the IPSS tool for MDS which is now the IPSS-R (see: My IPSS-R score)
6. Help to improve side effect management
7. Offer a way to research quality of life while studying a disease or the treatment of disease

A clinical trial falls into one of four phases:

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
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<tr>
<td>Phase I</td>
<td>This is the first time a drug is used in humans. The trial is designed to determine dosage, route of administration (oral, intravenous, or by injection), and schedule of administration (how many times a day or week). In this phase, researchers also begin to determine the drug's safety. The Phase I trial is normally conducted in healthy adults and enrolls only a small number of people (15-30).</td>
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<tr>
<td>Phase II</td>
<td>Patients with the disease receive the drug at dose levels determined in the earlier phase. The Phase II trial begins to determine the effectiveness of the drug and provides more information about its safety. Phase II trials usually include less than 100 people.</td>
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<tr>
<td>Phase III</td>
<td>The drug is tested alone or against an approved standard drug. The typical Phase III trial enrolls a large number of patients (100-thousands). If it is a comparison trial, patients may be randomly assigned to receive either the new drug or the standard intervention.</td>
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<tr>
<td>Phase IV</td>
<td>In Phase IV, the drug, already approved by the FDA and available to the public, undergoes continued evaluation in a large number of patients (several hundreds to several thousands). The Phase IV designation is rare.</td>
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</table>

Some trials, screening trials, and studies evaluating supportive care or prevention are not conducted in phases. In this type of trial, a group following a certain strategy to combat disease, such as a detection method or a behavioral change, is compared to a control group.
How is a clinical trial conducted?
Clinical trials may be conducted at a specific institution or as a part of a collaborative group. Each trial is assigned a lead researcher, known as the Primary Investigator (PI). You may meet some of the other members of the research team when participating in a clinical trial. They all work to be certain that your treatment follows the guidelines set out by the trial and that your safety is maintained.

Members of the research team
1. Lead physician, scientist, or nurse researcher—primary investigator (PI)
2. Other clinicians: physicians, nurse practitioners, or scientists (Sub-Investigators)
3. Statisticians
4. Research nurses
5. Data managers

How are clinical trials monitored?
Clinical trials for cancer treatment are overseen by a number of groups. The primary goals are to ensure patient safety and maintain rigorous scientific standards. These groups will review each clinical trial before the trial can be open for patient enrollment.

- Institutional Review Boards (IRB): A group of experts from the institution conducting the trial or representing a cooperative group of institutions who review each trial for patient safety and scientific merit. The IRB will continue to monitor the conduct of the trial until it is completed along with the Primary Investigator and the research team.
- Scientific Review Panels: A panel of experts who review clinical trials to ensure that they are based on sound scientific principles.
- Data and Safety Monitoring Boards: An independent committee of physicians, researchers, statisticians, and other experts.
- National Cancer Institute (NCI) and National Institutes of Health (NIH): Oversee selected clinical trials and maintain a list of registered trials. [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Key elements of a clinical trial
Patient protection: Patient safety is a primary focus for all clinical trials. The potential risks and benefits of each trial are reviewed carefully by a number of groups. You will be given a consent form which discusses the risks and benefits of the clinical trial in detail. Patient privacy is also a key component of patient safety. Data collected for the clinical trial will list patients by a study number and will only be shared with members of the research team who have signed a confidentiality agreement.

Informed consent: Before you can participate in a clinical trial, the research team must provide detailed information about the trial including the purpose of the trial, potential benefits and risks, the treatment plan (protocol and schedule), and your right to withdraw from the study at any time. You are encouraged to ask questions during this discussion so that you feel you understand the trial. You will then sign a consent form which provides this information and documents your informed consent.
Participating in a Clinical Trial

Am I a candidate for a clinical trial?
Each clinical trial has specific criteria for participation. These criteria ensure the specific research goals of the trial and patient safety criteria are being met. You will be screened for the trial before being enrolled to be sure these criteria are met. Additional testing will be conducted after you have signed the consent form for the trial. In some cases, after these tests are obtained, a patient may not meet the criteria for the trial and cannot proceed to treatment.

What questions should I ask about participating in a clinical trial?
These are most often answered during the informed consent process.

1. Why is the trial being done?
2. What are the potential benefits of the trial?
3. What is the potential risk of the trial?
4. What can I expect from day to day while I am on the trial? (Frequency of visits, types of testing, length of visits)
5. If I experience side effects, whom should I contact?
6. What are the costs of participating in the trial?
7. What other treatment options do I have if I do not participate in the clinical trial?
8. How long will I be in the trial?
9. What happens if the treatment is not working?

Clinical trials and drug approval information

European Medicines Agency
Decentralized agency of the European Union, located in London; responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union
www.ema.europa.eu

Health Canada
Provides a notice of compliance (NOC) for full approval of a new drug or an NOC with conditions in Canada
www.hc-sc.gc.ca

National Cancer Institute, National Institutes of Health
Registry and results database of federally and privately supported clinical trials conducted in the United States and around the world
www.clinicaltrials.gov

National Institute of Health and Clinical Excellence
Guidance for cost effectiveness of treatments for England and Wales
www.nice.org.uk

Nordic MDS Group
Provides Nordic guidelines for MDS management online and patient information in all Nordic languages
www.nmds.org

Pharmaceuticals and Medical Devices Agency
Regulation of drug availability in Japan
www.pmda.go.jp

Therapeutic Goods Administration
Division of the Australian government’s Department of Health and Aging; responsible for regulating therapeutic goods including medicines, medical devices, blood, and blood products
www.tga.gov.au

U.S. Food and Drug Administration
Approval required for commercial availability of therapy in the United States
www.fda.gov
Clinical Trials in MDS

An expanding number of experimental, or investigational, drugs are being evaluated for their potential use in treating MDS. Many trials are designed to find new targets in the MDS clone or the bone marrow microenvironment (see: What Happens to the Bone Marrow in MDS?). Other trials are investigating ways to combine currently available treatments with other novel agents. 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. Participation in a clinical trial may offer you a treatment option that would otherwise not be available to you. Some of the active clinical trials for MDS are included in the table below. Ask your provider if there are clinical trials that might be an option for you. The MDS Foundation’s Centers of Excellence provide options for clinical trial participation. Trials available at each center may vary. Additional information about clinical trials can be obtained by contacting the MDS Foundation, Inc. www.MDS-Foundation.org or The National Institutes of Health. www.clinicaltrials.gov.

References:
National Institutes of Health @ www.clinicaltrials.gov
How common is MDS in children?

MDS is primarily a disease of the elderly (most patients are older than age 65), but MDS can affect younger patients, as well. MDS in children is rare (1-4 cases per million per year). The median age at presentation in children is 6.8 years. It occurs equally in male and female children.

What causes MDS in children?

MDS can appear in an otherwise healthy child. Some evidence suggests that certain children are born with a tendency to develop MDS. This tendency or pre-existing factor can be thought of as a switch that can be triggered by external factors. The most common pre-existing factors in MDS are congenital (present at birth) and genetic (programmed in the cells) syndromes. These are present in about 50% of pediatric patients. If the external factor cannot be identified, then the disease is referred to as “primary MDS.”

MDS may also develop in a child with a known pre-existing condition, and is therefore called “secondary MDS.” Secondary MDS can be seen in children after chemotherapy or radiation therapy for another cancer. Children who take chemotherapy drugs or who receive radiation therapy for potentially curable cancers are at risk of developing secondary MDS for up to 10 years following treatment.

Secondary MDS is also seen with inherited bone marrow failure disorders such as Fanconi anemia or Diamond-Blackfan anemia, with acquired aplastic anemia, as well as with familial MDS. While this is extremely rare, some families seem to have a predisposition to develop MDS. It is a very rare occasion when family members, including siblings, are diagnosed with MDS. Factors that have been linked to the development of childhood MDS are listed below.

Factors and conditions that may predispose children to MDS

- Constitutional bone marrow failure abnormalities
- Fanconi anemia
- Kostmann syndrome
- Diamond-Blackfan syndrome
- Shwachman syndrome
- Down syndrome (trisomy 21)
- Neurofibromatosis type 1 (NF1) mutations
- Trisomy 8 mosaicism (some, but not all cells have an extra copy of chromosome 8)
- Congenital severe neutropenia
- Bloom syndrome
- Noonan syndrome
- Dubowitz syndrome
- Mitochondria cytopathy
- Familial MDS or leukemia
- Idiopathic aplastic anemia
- Prior chemotherapy (treatment-related MDS)

There are no known food or agricultural products that cause MDS. Children and their families often worry that MDS might be contagious. No evidence exists to suggest that a virus causes MDS, and MDS cannot be “transmitted” to loved ones.

What are the symptoms of MDS in children?

In the early stages of MDS, children may experience no symptoms at all. A routine blood test may reveal cytopenias (low blood counts). Sometimes the white cell and platelet counts may be low while the hematocrit remains normal. Children with MDS may present with nonspecific symptoms such as a pale complexion, fatigue, petechiae (tiny red or purple spots on the skin), or recurrent infections. In some cases, more severe symptoms such as shortness of breath, weakness, or bleeding may be present.
**Is MDS fatal?**

Failure of the bone marrow to produce mature healthy cells is a gradual process and therefore, MDS is not necessarily a terminal disease. However, some children do succumb to the direct effects of the disease and gradual bone marrow failure. A small number of the children diagnosed with MDS may progress to acute myeloid leukemia (AML).

Pediatric MDS can be quite variable in both the disease course and the outcomes. For example, some children with refractory cytopenia or low-grade RAEB can remain stable for many months or years, while others may rapidly become worse. Monosomy 7 in children is not associated with poor prognosis, unlike in adults; however, a few studies have suggested that children with monosomy 7 progress earlier to AML.

**How severe is my child’s MDS?**

Accurate classification of MDS is very important to help predict the course of your child’s disease, and is essential in guiding your child’s hematologist in selecting the best treatment. Because the disease course of MDS can vary widely from patient to patient, classification systems for grouping various “subtypes” of the myelodysplastic “syndromes” have been developed, and several classification systems are available that have been developed from those used for the adult forms of MDS (see: How Severe is My MDS?).

The adult World Health Organization (WHO) classification system has been revised to make it more applicable to pediatric MDS. The Modified WHO Classification for Pediatric MDS classifies myelodysplastic and myeloproliferative disorders into three major groups: (1) adult-type MDS, (2) Down syndrome–related disorders, and (3) juvenile myelomonocytic leukemia (JMML).

### Revised World Health Organization Classification of Childhood Myelodysplastic Syndromes (2008)

**Myelodysplastic Syndromes**
- Refractory cytopenia (RC)—blood blasts <2%, bone marrow blasts <5%
- Refractory anemia with excess blasts (RAEB)—blood blasts >2%, bone marrow blasts 5–19%
- Refractory anemia with excess blasts (RAEB–t)—bone marrow blasts 20–29%
- AML with MDS–related changes—peripheral blood or bone marrow blasts >20%

**Myelodysplastic/Myeloproliferative Disease**
- Juvenile myelomonocytic leukemia (JMML)

**Down Syndrome Disease**
- Transient abnormal myelopoiesis
- Myeloid leukemia of Down syndrome

**Down syndrome disease**

Approximately 10% of newborns with Down syndrome develop transient myeloproliferative disorder (TMD). In TMD there is an abnormally high number of immature white blood cells in the blood stream. Most children with TMD recover on their own within several weeks. A minority of children progress to a form of acute myeloid leukemia (AML) called M7–AML. Myeloid leukemia in children with Down syndrome is related to MDS, but has its own distinct features.

Blast cells from nearly all of these children have a specific abnormality in the gene that controls normal development of red blood cells and platelets. This mutation may prove to be useful in diagnosing the disease. M7–AML is very sensitive to chemotherapy. Children with TMD who develop M7–AML have a good response to AML chemotherapy.
Juvenile myelomonocytic leukemia (JMML)

The term JMML includes other childhood leukemias that were previously known as juvenile chronic myeloid leukemia, chronic myelomonocytic leukemia, and infantile monosomy 7 syndrome. JMML typically occurs at a very young age (less than 2 years) and is more common in boys. It is thought to represent about 25% of all pediatric MDS patients. JMML is often associated with other inherited diseases and other bone marrow failure syndromes. In JMML, many bone marrow stem cells develop into two types of white blood cells: monocytes and myelocytes. Some of these cells remain immature, or blast cells, and cannot carry out their normal functions. These excess build up in the bone marrow and get in the way of the manufacture of red and white blood cells, which can lead to anemia and infection.

Patients with JMML can have varying outcomes based on factors such as, age at diagnosis, number of blood platelets, level of fetal hemoglobin, or any changes in the chromosomes.

How do you treat MDS in children?

There are many considerations in the treatment of childhood MDS (see: General Principles of Treatment of MDS). Many of the strategies used to treat adults with MDS are being investigated in pediatric clinical trials (see: Clinical Trials). Allogeneic hematopoietic stem cell transplantation (HSCT) provides the best option for a cure (see: Bone Marrow Transplant).

How is MDS in children different than MDS in adults?

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Adult MDS</th>
<th>Childhood MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (million/yr)</td>
<td>&gt;30</td>
<td>0.5-4</td>
</tr>
<tr>
<td>Refractory anemia with ring sideroblasts (RARS)</td>
<td>20%-25%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Cytogenetic aberrations</td>
<td>30%-50%</td>
<td>50%</td>
</tr>
<tr>
<td>Mutation of Ras gene</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>5q- chromosomal aberration</td>
<td>20%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Monosomy 7 abnormality (seen in)</td>
<td>8%-10%</td>
<td>30%</td>
</tr>
<tr>
<td>Aim of therapy</td>
<td>Usually palliative</td>
<td>Usually curative</td>
</tr>
</tbody>
</table>

References:
Pediatric Information Resources—MDS and Childhood Cancers

Alex’s Lemonade Stand
Raises money and awareness for pediatric cancer causes, primarily for research into new cures and treatments
www.alexslemonade.org

American Cancer Society
250 Williams Street, NW
Atlanta, GA 30303
800-ACS-2345
www.cancer.org

American Society of Pediatric Hematology/Oncology (ASPHO)
4700 W. Lake Avenue
Glenview, IL 60025
847-375-4716
847-375-6475 fax
www.aspho.org

Aplastic Anemia & MDS International Foundation
100 Parl Avenue, Suite 108
Rockville, MD 20850
301-279-7202
800-747-2820
www.aamds.org

Blood & Marrow Transplant Information Network
2900 Skokie Valley Road, Suite B
Highland Park, IL 60035
847-433-3313 or 888-597-7674
847-433-4599 fax
www.bmtinfonet.org

Candlelighters Childhood Cancer Foundation
Provides information and awareness to support children with cancer and their families, and supports research
www.candlelighters.org

Childhood Leukemia Foundation
Supports children with cancer and their families
www.clf4kids.com

EWOG (European Working Oncology Group)
www.ewog-mds.org

JMML Foundation
9921 Carmel Mountain Road #170
San Diego, CA 92129
858-243-4651
www.jmmlfoundation.org

National Marrow Donor Program
3001 Broadway Street N.E., Suite 100
Minneapolis, MN 55413
800 MARROW2 (800-627-7692)
www.marrow.org

National Cancer Institute's Physician Data Query (PDQ) Comprehensive Cancer Database
Includes disease and treatment summaries for major types of pediatric cancers, including MDS
www.cancer.gov/cancertopics/pdq/cancerdatabase

National Cancer Institute's Clinical Trials Database
Listing of clinical trials for all types of cancer, including MDS
www.cancer.gov/clinicaltrials

Pediatric Myelodysplastic and Bone Marrow Failure Registry
Children's Hospital Boston
Department of Hematology
Fegan 7
300 Longwood Avenue
Boston, MA 02115 USA
Phone: 888-5-PediMDS
Email: MDS@childrens.harvard.edu
www.pedimds.org

Pediatric Oncology Resource Center
Resources for parents, friends, and families of children with cancer
www.acor.org/ped-onc

The Leukemia & Lymphoma Society
1311 Mamaroneck Avenue, Suite 130
White Plains, NY 10605
800-955-4572
www.leukemia.org

The MDS Foundation, Inc.
4573 South Broad Street, Suite 150
Yardville, NJ 08620
800-MDS-0839 (within US only)
609-298-1035 (outside US)
609-298-0590 fax
www.mds-foundation.org
Building Blocks of Hope is a global print and online patient advocacy initiative providing a personalized educational program for patients and caregivers to prepare, participate, and LIVE with MDS. The colors of the Building Blocks of Hope include Tucson Teal, Navajo Red, and Desert Sand. They are reminiscent of a Southwest landscape with the beauty of the night sky over the sand swept deserts and stunning mountain ranges. The colors represent welcoming, warmth, stability, healing, passion, and protection. These colors form the base for the Building Blocks of Hope logo constructed in a wave-like pattern indicating the fluidity of life, health and illness. The single red band which continues up into the plant symbolizes strength and improvement in bone marrow function. The idea of hope for the future and extension of life is emulated in the sprouting plant.

Building Blocks of Hope was created by Sandra Kurtin, Nurse Practitioner and Clinical Assistant Professor of Medicine and Nursing at the University of Arizona Cancer Center, Executive Committee and Board Member of the MDS Foundation, and advocate for patients and caregivers LIVING with hematological malignancies. The individual pages have been developed in collaboration with members of the International Nurse Leadership Board of the MDS Foundation and members of the MDS Foundation Board of Directors. Creative and technical support was provided by Adam Nichols and his team at Markations. Organizational and communications support was provided by Tracey Iraca, Sue Hogan, Lea Harrison and the MDS Foundation staff. Bone marrow illustrations provided by Kirk Moldoff.

A special thanks to our MDS patients and their caregivers for sharing their life experiences within their MDS journey. Additional thanks to the Executive Committee for the MDS Foundation, Peter Greenberg, M.D., Alan List, M.D., Stephen Nimer, M.D., and Pierre Fenaux,M.D., Ph.D., and to John Bennett, M.D. for ongoing contributions to the MDS Foundation. In memory of Bob Weinberg, who generously donated his time and legal expertise, and shared his own personal journey with MDS. Thanks to the scientists, health care professionals, and volunteers who continue to work towards improving the lives of MDS patients and their caregivers. To the countless numbers of patients and their caregivers who have participated and continue to participate in clinical trials that have led to a better understanding of and improved treatment strategies for MDS; we would not be where we are without your continued involvement. Thank you to our International Colleagues for their work in adapting the Building Blocks of Hope incorporating translation and integration of their culture for regions throughout the world.

We are grateful to all of our supporters; your contributions make the work of the MDS Foundation and support of patients and caregivers LIVING with MDS possible. A special thanks to my family for understanding my passion for this work.

We hope this project will provide a useful tool for health care professionals working with MDS patients. Most importantly, we hope the Building Blocks of Hope will empower MDS patients and their caregivers to LIVE with MDS.

Best regards and best wishes,
Sandy Kurtin