Building Blocks of Hope
A Patient and Caregiver Guide for LIVING with MDS

The International Nursing Leadership Board
and Board of Directors
The MDS Foundation

Created by Sandra Kurtin  www.buildingblocksofhope.com
The MDS Foundation
International Nurse Leadership Board
http://mds-foundation.org/nursing-leadership-board-nlb/

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• Sandra E. Kurtin, RN, MS, AOCN, ANP-C – Co-chair
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• Cindy Murray RN, MN, NP-adult
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  Cambridge, United Kingdom
• Jean A Ridgeway, MSN, APN, NP-C, AOCN
  Chicago, Illinois, United States
• Jayshree Shah, APN-C, AOCN, RN, MSN, BSN, BS, CCRP
  Hackensack, New Jersey, United States
• Natalie Singer, MSc, RN,BSc(Hons)
  Glasgow, Scotland, United Kingdom
• Mary L. Thomas, RN, MS, AOCN
  San Francisco, California, United States
• Sara M. Tinsley, ARNP, AOCN
  Tampa, Florida, United States
Building Blocks of Hope
Answering Common Questions About MDS

- Understanding the Diagnosis of MDS
- How is MDS diagnosed?
- What are my treatment options?
- What are the common side effects of treatment, and what can be done to control them?
- What new treatments are on the horizon to treat patients with MDS?
- What are the consequences of blood transfusion?
- Should I receive iron chelation therapy?
- How do I select a bone marrow transplant center?
- What can I do to keep myself healthy
Tools and Strategies for Success

- Explore the Building Blocks of Hope
  - Understand the disease
  - Know your IPSS and now IPSS-R risk category
  - Ask questions about treatment options
    - Schedule
    - Possible side effects
    - Strategies for managing them
  - Consider lifestyle, transportation

- Ask for help
- Become a partner in your MDS journey
- Build your MDS Plan
  - Learn to “track” your progress
What is MDS?

• The Myelodysplastic Syndromes (MDS) represent:
  - a group of bone marrow cancers
  - clonal (one cell line – in this case myeloid)
  - hematologic stem cell malignancies (cancerous cells that originate in the bone marrow)

• MDS is not one disease
  - rather a group of diseases originating in the bone marrow
  - with variations in clinical findings, disease trajectory, and treatment recommendations
What is MDS?

- What happens:
  - Cells are abnormal in shape/size: *Dysplastic*
  - Cells don’t work well: lead to *ineffective hematopoiesis*
  - Result is *cytopenias* – low blood counts
  - There is a risk of developing leukemia in some cases (leukemic transformation)

- In general, as the disease progresses, bone marrow function declines
All Blood Cells Begin as Hematopoietic Stem Cells

Healthy Bone Marrow

1. Hematopoietic stem cell
2. Multipotential stem cell
3. Myeloid progenitor cell

- Natural killer (NK) cells
- T lymphocytes
- B lymphocytes
- Neutrophils
- Basophils
- Eosinophils
- Monocytes/macrophages
- Platelets
- Red blood cells
In MDS, Defects in the Bone Marrow Environment and Cells Lead to Ineffective Hematopoiesis

Intrinsic and extrinsic factors create defects in normal hematopoiesis.

MDS Bone Marrow

Hematopoietic stem cell

Lymphoid progenitor cell

Multipotential stem cell

Myeloid progenitor cell

Natural killer (NK) cells

T lymphocytes

B lymphocytes

Neutrophils

Basophils

Eosinophils

Monocytes/macrophages

Platelets

Red blood cells

Peripheral cytopenias

Hypercellular bone marrow

Immature precursor cells

Stem cell basics. National Institutes of Health Stem Cell Information Web site.

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How Is MDS Diagnosed?

- Peripheral blood counts + reticulocyte count
- Bone marrow biopsy and aspiration
  - Hematopathology
  - Bone marrow blasts (%)
  - Cellularity
  - Dysplastic features
  - Cytogenetics
  - Iron stain
  - Reticulin stain
- Additional tests
  - Iron saturation, ferritin
  - B12, folate levels
  - EPO level
  - Hemolysis screen
  - TSH, testosterone
  - Renal and hepatic profiles

Establish diagnosis of MDS
Determine subtype
FAB/WHO
Estimate prognosis
IPSS score

EPO = erythropoietin; FAB = French-American-British; WHO = World Health Organization; TSH = thyroid; IPSS = International Prognostic Scoring System.
# Myelodysplastic Syndromes: Classification Systems

<table>
<thead>
<tr>
<th>FAB</th>
<th>WHO</th>
<th>WHO 2008</th>
<th>DYSPLASIA</th>
<th>BLAST % (BM/PB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia (RA)</td>
<td>RA</td>
<td>RC with unilineage dysplasia (RCUD) RA</td>
<td>Erythroid Nonerythroid Nonerythroid Erythroid + other Erythroid + megakaryocytic Unilineage + pancytopenia or RCMD/RCUD with 1% PB blasts</td>
<td>All: &lt; 5/≤ 1</td>
</tr>
<tr>
<td></td>
<td>Myelodysplastic syndromes, unclassified (MDS-U)</td>
<td>Refractory neutropenia Refractory thrombocytopenia RCMD Isolated del(5q) MDS-U</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Refractory cytopenia with multilineage dysplasia (RCMD) Del(5q)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>RARS RCMD-RS</td>
<td>RARS RCMD-RS</td>
<td>Erythroid only Erythroid + other (all &gt; 15% RS)</td>
<td>&lt; 5/&lt; 1</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts (RAEB)</td>
<td>RAEB-1 RAEB-2</td>
<td>RAEB-1 RAEB-2</td>
<td>≥ 1 lineage ≥ 1 lineage</td>
<td>5–9/2–4 10–19/5–19 ± Auer rods</td>
</tr>
<tr>
<td>RAEB in transformation</td>
<td>Acute myeloid leukemia (AML)</td>
<td>AML</td>
<td>Myeloid ± other</td>
<td>≥ 20/—</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia (CMML)</td>
<td>MDS/myeloproliferative disorder (MPD) CMML Juvenile MML (JMML) Atypical chronic myeloid leukemia (aCML) MDS/MPD-U</td>
<td>MDS/myeloproliferative neoplasm (MPN) CMML JMML BCR-ABL–negative CML MDS/MPD-U</td>
<td>Variable &gt; 1 × 10⁹/L monocytosis</td>
<td>All: &lt; 20/—</td>
</tr>
</tbody>
</table>

From: Ridgeway et al, 2012
The International Prognostic Scoring System (IPSS and IPSS-R)

- System for estimating expected survival without treatment and risk of developing leukemia
- Disease related factors associated with risk/prognosis
  - Blast %, Cytogenetics, Cytopenia
  - International Prognostic Scoring System (IPSS) and more recent revised IPSS (IPSS-R)
- Primary consideration is selecting treatment
The manuscript describing the Revised IPSS (IPSS-R) for MDS is available now at Blood Online (June 27, 2012, (vol.120, p2454) OR on the MDSF website

http://www.mds-foundation.org/ipss-r-calculator/

http://www.ipss-r.com

An iPhone App for the IPSS-R calculator tool is also accessible through the Apple Store (enter MDS IPSS-R)
The Facts About MDS

• The average age at diagnosis is 73 years
• MDS remains an incurable *malignancy* for the majority of patients
• Allogeneic-HCT is the only potential “cure”
• The leading cause of death is the disease itself (~80%)
• Risk-stratified treatment strategies are key to optimal therapeutic outcomes

Dayyani et al., 2010; Kurtin et al, 2012
Individualized Treatment

• Treatment Triggers: Initiation of disease modifying therapy
  o Transfusion dependence
  o Progressive or symptomatic cytopenias
  o Increasing blasts
  o High-risk disease

• Individualized treatment selection
  o Performance status (good vs poor)
  o Comorbidities
  o IPSS risk category (low/Int-1 vs Int-2/high)
    • Low/Int-1: improve hematopoiesis
    • Int-2/high: survival
  o Primary vs secondary MDS
  o Cytogenetic status (del[5q], complex karyotype)
  o Lifestyle
What Are the Current Treatment Options?

- Supportive care: Transfusions, growth factors
- REVLIMID® (lenalidomide)
- VIDAZA® (azacitididine for injection)
- Dacogen® (decitabine)
- Chemotherapy: Cytarabine, Clofarabine, Etoposide
- Bone marrow transplant
- Investigational agents

FDA approved agents are limited
Maximizing each option to its full benefit is critical
# Mechanisms of Action of Therapies Under Investigation

<table>
<thead>
<tr>
<th>AGENT</th>
<th>TARGET</th>
<th>MOA</th>
<th>TRIAL/POPULATION</th>
<th>RESPONSE</th>
<th>GRADE 3/4 AES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRY-614&lt;sup&gt;a&lt;/sup&gt;</td>
<td>P38/Tie-2</td>
<td>Antineoplastic, anti-inflammatory, and antiangiogenic activity</td>
<td>Phase I/low or Int-1 risk (N = 100)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
| Entinostat (SNDX-275/MS-275)<sup>b</sup> | Histone DAC | Class 1 HDAC1 and HDAC3 inhibitor | Combination with azacitidine; phase III/high risk (N = 150)<sup>c</sup> | HR and CyR did not differ between AZA/Pbo versus AZA/entinostat | • Thrombo: 63%  
  • Fatigue 23% |
| Erlotinib<sup>d</sup> | EGFR signaling leads to DNA synthesis and proliferation | Tyrosine kinase inhibitor that blocks EGFR signaling | Phase II/Int-2 and high risk (N = 24)<sup>e</sup> | ORR: 17% | • Diarrhea: 21%  
  • Thrombo: 17%  
  • Rash: 17% |
| Everolimus (RAD-001)<sup>f</sup> | mTOR | Inhibitor of mTOR that induces G₁ arrest | Phase II/low and Int-1 risk (not yet recruiting)<sup>g</sup> | – | – |
| Ezatiostat<sup>h</sup> | GST P1-1 | Stimulates proliferation of myeloid precursors | Phase I/Int-2 (N = 45) | HI: 38% | • Neutropenia: 7% |
| ON-0110.Na<sup>i</sup> | Polo-1 kinase, PI3K, AKT | Inhibits mitotic progression and induces apoptosis | Phase II/Int-1, Int-2, high risk (N = 10)<sup>j</sup> | ORR: 50% | • GI: 10%  
  • Dysuria: 10%  
  • Fatigue: 10%  
  • Epistaxis: 10%  
  • No heme toxicities |
| Panobinostat (LBH589)<sup>k</sup> | Histone DAC | Pan DAC inhibitor, inhibits differentiation and induces apoptosis | Phase II/relapsed or refractory MDS (N = 10)<sup>l</sup> | 70% had stable disease | • Thrombo: 80%  
  • Neutropenia: 70%  
  • Leukopenia: 60%  
  • Anemia: 50%  
  • Febrile neutropenia: 20% |

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<sup>a</sup> P38/Tie-2.  
<sup>b</sup> Histone DAC.  
<sup>c</sup> Entinostat (SNDX-275/MS-275).  
<sup>d</sup> Erlotinib.  
<sup>e</sup> EGFR signaling leads to DNA synthesis and proliferation.  
<sup>f</sup> Everolimus (RAD-001).  
<sup>g</sup> mTOR.  
<sup>h</sup> Ezatiostat.  
<sup>i</sup> ON-0110.Na.  
<sup>j</sup> Panobinostat (LBH589).  

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From: Ridgeway et al, 2012, CJON  
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Key Principles of Therapy in MDS

• Allogeneic bone marrow transplantation remains the only potential cure.
  - This is not an option for the majority of patients due to co-morbidities and availability of a suitable related donor

• Age alone should not exclude active therapies
  - Consider performance status and comorbidities

• All active therapies for MDS require time to work (4-6 months of continued treatment)

• Blood counts often get worse before they get better

• Pro-active management of side effects in the early phases of treatment are key to obtaining the best response
Why Is Time Required?
Consider What is Happening...

• Blood counts drop as MDS progresses, and normal blood cells are crowded out by abnormal stem cells in the bone marrow and blood.
Why Is Time Required?
Consider What is Happening...

...When Treatment is Initiated

- As the treatment “cleans” the marrow, blood counts may drop further. Patients may experience hematologic toxicities

ANC (Neutrophil Granulocytes)

ANC, 10⁹/L

ANC ref. value

ANC Mean ± 97.5 CI

Why Is Time Required?
Consider What is Happening...

...As The Patient Begins to Respond

- The bone marrow begins to recover, allowing it to make healthy blood cells. Blood cell counts should rise and symptoms of MDS should improve.
Why Is Time Required?
Consider What is Happening...

...As The Response Continues

- Patient can be weaned from supportive care as a robust response sets in.

ANC (Neutrophil Granulocytes)

<table>
<thead>
<tr>
<th>Treatment, weeks</th>
<th>ANC, 10^9/L</th>
<th>ANC Mean ± 97.5 CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>2.2</td>
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<tr>
<td>11</td>
<td>1.7</td>
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<tr>
<td>16</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

ANC ref. value

The Challenge is Getting Through the First Few Cycles

Early toxicities may be difficult and/or discouraging for the patient...

ANC (Neutrophil Granulocytes)

Treatment, weeks

ANC Mean ± 97.5 CI

KEY PRINCIPLES OF THERAPY FOR MDS

- Time is required for the best response: A minimum of 4-6 months
- Cytopenias often get worse before they get better
- There are strategies for getting through the initial cycles of therapy
  - Dose modifications/delays
  - Supportive care
  - Setting expectations

Working together for the best response

Before Treatment Begins
When Treatment is Initiated
As The Response Continues
As The Response Continues

Trilineage Response Following 4 Cycles of Azacitidine

- Hgb (g/dl) and WBC (cells/μl)
- Platelet (cells/μl)

Referral, Evaluation, Diagnosis, and Observation
Cycle 1 9/20/10
Cycle 2 10/18/10
Cycle 3 11/15/10
Cycle 4 12/14/10
HCT 1/24/11

Started treatment with cytopenias “Fix the factory”
Increased transfusion needs prior to response “Worse before better”


Copyright 2012 - Building Blocks of Hope
Patient Response Over 10 Years of Lenalidomide Treatment
Sustained Moderate But Asymptomatic Cytopenias–A New “Normal”
What Can I do To Stay Healthy?

- Balanced Diet
- Daily Activity/Exercise
- Avoid Infection
- Avoid Bleeding
- Continue to Enjoy Things You Love - *LIVE*
- Get Enough Rest
- Take Advantage of Available Resources
  - Explore the Building Blocks of Hope
- Ask for Help When Needed
- Be an Active Participant in Building Hope
Healthy Body Healthy Mind


Becoming a Partner in Your Care:

Building Your MDS Plan
The 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 \textit{LIVE} with MDS

\url{http://www.mds-foundation.org/bboh2/}
Building Blocks of Hope
Online Interactive Format

• Most interactive and versatile
• View the complete handbook in a beautiful page-turning format; listen to embedded videos and watch slide presentations presented by leading experts in MDS.
• Use a search feature and thumbnail views to quickly find the information you are looking for.
• Access numerous patient and caregiver resources by using the embedded hyperlinks.
• Create a custom handbook by printing individual pages that include information that specifically applies to the individual patient.

http://buildingblocksofhope.com/
Building Blocks of Hope
Online Interactive Format for the Patient

• Create a personalized MDS Plan (page 92-98)
  o a working document that allows you to create an individualized profile:
    • about your MDS diagnosis
    • your health profile
    • members of your health care team.

• Tools for tracking your progress are included (page 85-91)
  o Place these resources in a three-ring binder and add additional pages as needed, laboratory or radiology results, and any other information you find useful to take to your health care provider visits. This will provide a great tool for taking an active part in your care.
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Links to Online Resources are included throughout

PDF format – not interaction but can be saved as i-book on I-pad or Kindle

MDS Patient Outreach and Advocacy Program

Patients or caregivers may contact the patient liaison directly by calling (toll-free) 800-637-0839 or via e-mail to ahassan@mds-foundation.org
Tab 1: Understanding MDS:
• A complete description of the disease process of MDS and answers to common questions.

Tab 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.

Tab 3: Quick Tips:
• The quick tips offered in this section include guidelines for monitoring and managing your symptoms.

Tab 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.
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Tab 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*
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Tab 6—The MDS Foundation:

- The MDS Foundation is an international publically 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.
  - Online and live patient and caregiver support
  - Coordination and support of the patient and caregiver forums
  - Print and digital global educational resources
  - Coalition of Centers of Excellence
  - Planning and facilitation of a biannual international scientific meeting dedicated to scientific developments in understanding MDS, finding new treatment options, and improving the quality of life for patients and caregivers living with MDS.
Let's Talk About You