MDS: Understanding Your Diagnosis and Current and Emerging Treatments

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Objectives
- Overview of:
  - Bone Marrow Function and Blood Cell Production
  - General Leukemia Concepts
- MDS Basics:
  - What is MDS?
  - Who gets it?
  - What causes it?
  - Classification
    - WHO
    - IPSS/R
    - Lower Risk
    - Higher Risk

MDS Treatment:
- Lower Risk:
  - Observation
  - Transfusions
  - Growth Factors
  - Immunotherapy/Immune modulatory
- Higher Risk:
  - Transfusions
  - Hypomethylating agents
  - Induction Chemotherapy
  - Transplant

Hematopoiesis = Blood Cell Production

Normal Bone Marrow Function and Blood Cell Production Requires.....
A Deeper Look at the Bone Marrow Factory

General Leukemia/MDS Concepts

Description of Bone Marrow Cancers

By How They Grow:

**Acute:** FAST Growth + Cells Don’t Grow Up + Cells Don’t Die When They Should
→ Bone marrow factory dysfunction → Too many blasts and not enough normal RBC, WBC, platelets

**Chronic:** Fast Growth + But...Cells DO Grow Up and DO Die When They Should
→ All stages of bone marrow and blood cells present but overgrowth of the specific cancer cell

Description of Bone Marrow Cancers

By How Patients Present:

**Acute:**
- Very sudden onset
- Very sick at presentation

**Chronic:**
- Gradual onset: Sneaks up on patient
- Patient not usually ill
- Often discovered on routine exam

Classification of Bone Marrow Cancers: MDS and AML (Myeloid Disorders)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blasts (%)</th>
<th>Blood counts</th>
<th>Myelodysplasia</th>
<th>Splenomegaly</th>
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<tr>
<td>AML</td>
<td>&gt;20%</td>
<td>Decreased or Increased with blasts</td>
<td>+/-</td>
<td>+/-</td>
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<tr>
<td>MDS</td>
<td>&lt;20%</td>
<td>Decreased</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>MPN</td>
<td>&lt;20%</td>
<td>Increased (decreased with splenomegaly)</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>MDS/MPN</td>
<td>&lt;20%</td>
<td>Increased</td>
<td>+/-</td>
<td>+/-</td>
</tr>
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</table>

MDS
“MDS: What is it?”

- Bone Marrow (Blood Factory) Cancer:
  - The blood factory makes lots of blood cells (Red Blood Cells + White Blood Cells + Platelets)
  - But, in MDS the cells don’t work right and don’t live a normal lifespan
  - So, blood counts are low
  - Increased risk of infection
  - Possible progression to acute leukemia


<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Both Sexes</th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>Count</td>
<td>Rate</td>
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<tr>
<td>All Races</td>
<td>4.9</td>
<td>21,338</td>
<td>6.7</td>
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<tr>
<td>White</td>
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<tr>
<td>Black</td>
<td>4.1</td>
<td>1,617</td>
<td>5.3</td>
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<tr>
<td>Asian/Pacific Islander</td>
<td>3.7</td>
<td>1,420</td>
<td>4.8</td>
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<td>American Indian/Alaska</td>
<td>3.4</td>
<td>76</td>
<td>3.6</td>
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<tr>
<td>Hispanic</td>
<td>3.5</td>
<td>1,644</td>
<td>4.4</td>
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</table>

“MDS Pathogenesis

- Genetic Event
- Epigenetic Modulation
- Bone Marrow Stem Cells

Early/Low Risk Disease
- Cell Growth + Cell Death
- Cells don’t grow up
- Low Blood Counts

MDS: Why Does it Happen?”

- Idiopathic/de-novo: “We don’t know why”
  - Majority of cases
- Secondary: linked to known exposure and account for 20-30% of cases
  - Chemotherapy
  - Radiation Therapy
  - Benzene
  - Viral infections (possible)
  - Tobacco/ETOH (possible)
  - Immunosuppressive therapy (possible)

“MDS: Why Does it Happen?”

- Treatment Related:
  - Two Major Forms:
    - Early:
      - Onset 1-3 years after chemotherapy
      - Associated with specific chemotherapy drugs used in breast cancer therapy, lymphoma therapy
      - Associated with the 1q23 cytogenetic abnormality
    - Late:
      - Onset 5 – 7 years post therapy
      - Associated with specific chemotherapy drugs used in lymphoma therapy or radiation therapy
      - Associated with chromosome loss and often monosomy 5 or 7
“What does it look like?”

- Clinical Symptoms: Related to Low Blood Counts
  - Anemia (low red cells): Fatigue, pale, trouble breathing, weakness
  - Thrombocytopenia (low platelets): increased bruising or bleeding
  - Neutropenia (low infection fighting white cells): increased infections

How do we treat it?
How do we decide which treatment approach is best?

Patient Treatment Goals

+ Use MDS Classification and Prognostic Scoring Systems

MDS: Patient Treatment Goals

- Supportive wishes only:
  - transfusions, growth factors, minimal medical interventions
- “Disease Modifying” Treatments:
  - Treatments that may change the natural history of the MDS but don’t “cure” it
- “Curative” Therapy:
  - Stem Cell Transplant

MDS Classification Systems

The Most Current Classification Systems

WHO Pathology Classification

Classification that the pathologist completes when looking at your bone marrow biopsy
This is the “name” or subtype of your MDS

WHO Pathology Classification 2008
WHO Pathology Classification: 2016

Prognostic Classification

Risk Stratification that your oncologist does in the clinic to help further guide treatment decisions.

MDS Risk Assessment: The First IPSS Classification System: 1997

Cytogenetics = Karyotype = Chromosome Analysis

IPSS Classification System

Attributes:
- Simple score calculation to predict prognosis and help guide treatment decisions

Limitations:
- Cytogenetic risk groups oversimplify the categorization of the numerous known MDS abnormalities
- Based on untreated de-novo MDS patients at diagnosis so applicability to t-MDS unknown
- Not dynamic. Typically done just at “diagnosis”

Revised IPSS: 2012

Table 1. IPSS and RAS features and categorization of MDS

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Overall Score</th>
<th>Risk of Progression (%)</th>
<th>RAS, Cytogenetics (atrophy)</th>
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<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>97%</td>
<td>0%</td>
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<tr>
<td>Int-1</td>
<td>0.5-1.0</td>
<td>55%</td>
<td>9%</td>
</tr>
<tr>
<td>Int-2</td>
<td>1.5-2.0</td>
<td>25%</td>
<td>11%</td>
</tr>
<tr>
<td>High</td>
<td>&gt;2.5</td>
<td>5%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Risk Factors:
- MDS subtype
- Baseline karyotype
- Cytogenetic abnormalities

Revised International Prognostic Scoring System for Myelodysplastic Syndromes

Table 1. Revised IPSS score value

<table>
<thead>
<tr>
<th>Score</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

- A: MDS subtype
- B: Baseline karyotype
- C: Cytogenetic abnormalities
- D: Other factors

Risk of Progression (at diagnosis): 0% to 30%
IPSS-R Categories Impact on Survival

Improvements in Cytogenetic Categorization
- IPSS-R: 5 Category System (improved from prior 3 category system)

Survival Differences of IPSS-R Categories Based On Age
- Importance of IPSS-R AND Age on personalized treatment decisions

Molecular Classification: New Methods of Classification

What Does Molecular Analysis Mean??

Refinements in Risk Prediction: Molecular Signatures
Added Benefit of Molecular Signature to IPSS Scoring Predictions

That’s a LOT of Naming and Risk Stratifying…….

- Why is all this classification needed?
- Very different clinical outcomes depending on the type and characteristics of the MDS:
  - Very indolent disease ➔ Explosive disease progressing to AML
- Until recently we only had supportive therapies but now treatments range from controlling the disease to cure
- Curative therapy carries higher risk so important to balance risk of disease with risk of the treatment

Treatment Options

- Decided by patient treatment goals + WHO/IPSS risk stratification

Treatment Decision-Making

Treatment for Low Risk MDS

- Observation
- Supportive Care
- Transfusions
- Growth Factor Support
- Lenalidomide
- Immune Therapy

Overall Treatment Goal:
- Supportive Care or Observation Only
- Disease Modifying Treatment (when do we start?)
- Potentially Curative Therapy: Stem Cell transplant
- If transplant is planned need to determine:
  - Timing of transplant: early or delayed
  - Pre-transplant therapy is needed

Once treatment goals established then a treatment strategy (and timing to start treatment) is developed based on:
- Current MDS Status:
  - Risk: WHO Pathologic Classification/IPSS Risk
  - Current MDS impact on quality of life
When do we use observation?

- The decision to treat MDS depends on the impact that the MDS is having on the patient.
- We want to balance the risk of the MDS with the risks of the treatment intervention.
- If the blood counts are just mildly low, no transfusions are needed, there are no infections, and the risk stratification is low then there is no benefit to starting treatment because the risk of the treatment/side effects of treatment will be greater than the risk of the MDS.
- Observation appropriate when:
  - Risk of Treatment
  - Risk of MDS.

Supportive Care: Transfusions

Help Relieve symptoms but don’t fix underlying bone marrow problem.

Transfusions Limited by:
- Availability of correct blood type
- Increase Risk for iron build up in body

Growth Factors: Red and White Cell Boosters

- **RBC Stimulators:**
  - Goal: Boost RBC production for those with low EPO levels.
  - **White Blood Cell Stimulator**
    - Neupogen or Neulasta
    - Used when active infection.

Growth Factors: Platelet booster

- **Promacta:** Pill Platelet stimulator
  - Currently FDA approved for:
    - Aplastic Anemia
    - Hepatic induced Low Platelet
  - Use in MDS:
    - Phase I testing showed improvement in platelet and red blood counts.

Iron Overload: Result of too many red cell transfusions

- Baseline ferritin and iron studies should be checked prior to starting transfusions.
- Each transfusion holds 250 mg of iron.
- Our bodies get rid of only approximately 1-2 mg of iron a day.
- The risk of iron overload and deposition into the organs increases after around 20 units of blood.
- How do we deal with this? — Iron Chelation Therapy.

Iron Chelation Therapy

- **Used In:**
  - Lower Risk transfusion-dependent MDS
  - Patients with > 20 RBC transfusions and expected ongoing needs
  - Ferritin level > 2000
- **Treatment Options:**
  - **Deferoxamine:** SQ infusion given over about 12 hours overnight approximately 3 nights a week.
  - **Deferasirox:** (Exjade or Jadenu) Oral medication
    - Black box Warning: Increased risk of hepatic and renal failure and GI bleeds in certain populations including high-risk MDS.
  - **Deferiprone:** Newer oral agent
    - Black box warning for agranulocytosis.
MDS “Disease Modifying” Treatment Options

“Disease Modifying” Therapies
- Azacitidine: FDA Approved May 2004
- Lenalidomide: FDA Approved in December 2005 for Low/INT-1 risk with 5q- phenotype
- Decitabine: FDA Approved May 2006
- What has happened since 2006???

Disease Modifying Treatments for Lower Risk MDS
- Immune Modulatory Drugs + Lenalidomide
- Immunosuppression: ATG + CSA

Treatment Decision-Making

5q minus Syndrome
- Syndrome of refractory macrocytic anemia with normal to elevated platelet count and retained neutrophil count
- Typically occurs in middle age/older women
- Bone marrow with micromegakaryocytes, < 5% blasts, and cytogenetics showing isolated 5q deletion
- Clinical Course: Relatively benign clinical course over years with varying need for PRBC transfusions
Lenalidomide in del 5q31: Transfusion Independence

**Benefits:**
- High response rate of transfusion independence in Low/INT-1 pts with isolated 5q minus
- Relatively quick time to response
- Initial Cytopenias (drop in platelets and neutrophils) appear to predict who will respond
- Oral/outpatient regimen

**Drawbacks:**
- Potential for significant neutropenia/thrombocytopenia
- Chronic therapy until progression or intolerance
- Not curative

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**Lenalidomide Summary**

- **Response Rate** = 30%
- Chance of response increased if:
  - Younger
  - HLA DR15
  - Lower-Risk IPSS

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**ATG + CSA**

Older therapy option
Not used as often now
Disease Modifying Treatment for Higher Risk MDS

Treatment Decision-Making

Azacitidine “Epigenetic” therapy

Azacitidine
- First treatment for MDS (besides transplant) that was able to change the natural course for MDS patients
- Improved patient survival
- Decreased chance of progression to acute leukemia
- Improved quality of life
- Well tolerated in even older and sicker patients
- Responses seen even in highest risk MDS
- Chronic Therapy

Azacitidine
- “Hypomethylating agents”
  - Slower Acting Chemo: can take a few months to see a response
  - Goal: “fix” the abnormalities in the bone marrow cells that caused the MDS
  - Improve blood counts and decrease transfusion needs
  - Chronic Therapy: once response is seen treatment continues until response stops or side effects not tolerable
What to Expect: Azacitidine

- Standard Treatment: Cycle = Daily injections for 5-7 days in a row repeated every 4 weeks. Can be given through an IV or as a shot under the skin. Dose schedule can be changed depending on your specific medical situation and treatment goals.
- Common Side effects:
  - Low blood counts: Blood counts drop in the first couple cycles before you see the response.
  - Gastrointestinal changes: constipation, diarrhea, or nausea.
  - Fatigue.
  - Fever.
  - Skin changes/Rash (more with shot administration).
  - Aches in the joints.

What to Expect with Azacitidine: Response Rates

- Overall Clinical Response Rates: 35-50%.
- Improved blood counts (most common).
- Complete Remission = bone marrow looks normal and blood counts are normal (less common).
- Improves Overall Survival.
- Delays time to development of acute leukemia.
- Improves quality of life in those patients who respond.

Azacitidine: Summary

- Benefits:
  - Well tolerated even in older patients with other medical issues.
  - Outpatient treatment.
  - Improves survival, delays transformation to acute leukemia.
  - Improves quality of life.
  - Responses seen even in the most high risk groups (those patients with high risk bone marrow chromosome changes).
- Drawbacks:
  - Can take months to see a response so requires patient and doctor patience to allow chance to see response.
  - Chronic therapy: continuous monthly therapy as long as benefit and minimal toxicity.
  - Not a “cure.”

Decitabine

Another Hypomethylating Agent.
“Sister” Drug to Azacitidine.
How do Azacitidine and Decitabine Compare?
Comparison Between Decitabine and Azacitidine for the Treatment of Myelodysplastic Syndrome: A Meta-Analysis With 1392 Participants

<table>
<thead>
<tr>
<th>Outcome (Partial Remission)</th>
<th>Azacitidine</th>
<th>Decitabine</th>
<th>P</th>
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<tbody>
<tr>
<td>C3 (Complete Remission)</td>
<td>41/177 (23%)</td>
<td>31/177 (18%)</td>
<td>0.30</td>
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<tr>
<td>C1 (Complete Remission)</td>
<td>107/177 (60%)</td>
<td>75/177 (42%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>C0 (Complete Remission)</td>
<td>84/177 (47%)</td>
<td>56/177 (31%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Total (Complete Remission)</td>
<td>222/177 (125%)</td>
<td>152/177 (86%)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Clinical efficacy in myelodysplastic syndrome

Induction Chemotherapy for MDS: What is this and when is it appropriate?

- Induction Chemotherapy: Acute leukemia type chemotherapy given in the hospital
- "Atomic Bomb" type chemo with a goal to wipe out most of the bone marrow (blood cell factory) and hopefully get rid of most of the MDS in the process
- Counts drop down very low requiring red cell, platelet transfusions, and increasing infection risk
- 1 month hospital stay
- Higher risk up front life threatening complications (around 10-15%) BUT higher and faster reward (quicker time to response)
- Appropriate to use this in patient’s whose MDS is behaving aggressively, moving fast, and is likely to be too fast to respond to the slower hypomethylating agents. Also appropriate in those whose ultimate plan is to move to stem cell transplant and have large blast burden

Newer Therapies being tested in Clinical Trials
**MDS Therapies in Development**

**Potentially Curative Therapy**

**Hematopoietic Stem Cell Transplant**

- **Allogeneic Bone marrow transplant** only definitive/cureative treatment available with 2-3 year disease free survival ranging from 30-70%

- Patient eligibility limited by:
  - Age
  - Performance status
  - End organ function
  - Availability of donor

- Numerous Controversies regarding transplantation in MDS exist:
  - Timing: Early versus Delayed
  - Optimal Disease burden at transplant
  - Pre-transplant therapy
  - Conditioning therapy
  - Donor Source

- Use of reduced intensity conditioning (“Mini”) transplants expanding curative potential to older “fit” patients
“First things first: What is a Stem Cell?”

- Blood Stem Cells = Cells in the bone marrow (blood cell factory of your body) that make all the blood cells (white blood cells, platelets, red blood cells) for your entire life
- This is the cell that is “messed up” in MDS and AML so that normal blood cells are not made and transfusions are needed

“A Deeper Look at the Bone Marrow Factory”

“What is a Stem Cell Transplant?”

- Two Step Process:
  - “Conditioning”: Using chemotherapy +/- radiation to “get rid” of the MDS/AML cells in the bone marrow and make room for the new stem cells to grow and replenish the blood supply
  - “Transplant”: Infusion of the donor stem cells via IV into the blood and they make the trip to the bone marrow to start producing blood cells

“How is a stem cell transplant a possible cure?”

- There are two ways that a transplant works:
  - The “conditioning” (given before the stem cell infusion) decreases the amount of MDS or AML in the body (likely the less important part of the process)
  - The new stem cells, not only create the red blood cells and platelets, but in making new white blood cells, create a new immune system.
    - The new immune system is what gets rid of the remaining MDS/AML cells that the chemotherapy couldn’t

“Why don’t we do stem cell transplants for everyone?”

- Not everyone has a donor:
  - Becoming less of an issue with cords and “haplo” donors
- Not everyone is “fit” enough to undergo the treatment due to other medical problems
- The transplant is not a guaranteed cure
  - “Cure” rates range from 30-70% depending on the type of MDS/AML and the status of the MDS/AML at transplant
“If the risks are that high, why do we consider transplant?”

- It comes back to balancing risk.
- Risk of the disease (MDS) AND risk of the treatment (transplant):
  - If the risk of a life altering complication due to MDS is higher than the risk from the transplant, then it makes sense to consider the transplant.

“What do we do after we have decided that a stem cell transplant makes sense?”

- Find a stem cell donor:
  - Brother or sister
  - Unrelated adult (national marrow donor registry)
  - Umbilical cord blood
- Clinical Evaluation to see if patient is “fit enough” to proceed
  - Heart, lung, liver, kidney testing
- Transplant: Hospital stay of 3-6 weeks for “conditioning therapy,” transplant infusion, and monitoring for count return and for complication
  - Close follow-up in bone marrow transplant clinic
  - Classify as “cure” if still in remission at 2 years post transplant

MDS Treatment Summary

- Complicated blood cell factory disorder that can range from mild form to aggressive acute leukemia type illness
- Treatment Decision-making depends on severity and symptoms:
  - To treat or not to treat?
    - Which would cause more symptoms? The MDS or the treatment?
  - Treatment choice depends on:
    - Age, Risk scores, Chromosome changes, activity level, treatment goals
  - Very individualized and sometimes quite challenging
  - At least now we have more options……………………

Questions?