Overview

- Review MDS Definition
- Define Higher Risk MDS
  - IPSS and WHO scoring systems
- Discuss Treatment Strategies for high risk MDS
  - Hypomethylating Agents: Azacitidine and Decitabine
  - Intensive Chemotherapy
  - Stem Cell (aka Bone Marrow) Transplant
  - Clinical Trials
“MDS: What is it?”

- Variable and complex group of bone marrow stem cell disorders with wide range of clinical severity with the following features:
  - Dysplastic or “funny looking” blood cells
  - Low blood counts
  - Increased risk of infection
  - Varying degree of risk for transformation to acute leukemia (AML)

“How Does MDS Develop?”

- Lower Risk MDS:
  - Bone Marrow Cell Growth + Cell Death
  - Blood Cells don’t “grow-up”

- Higher Risk MDS:
  - Bone Marrow Cell growth + Cell death
  - Blood cells don’t “grow up”

- Genetic Event: Chromosome Damage
- Epigenetic Modulation
“How Do We Classify MDS?”

FAB 1970-1980’s
IPSS 1997
WHO Initially 1999
Updates 2002 2008
WPSS “Time Dependent Scoring system” 2007

IPSS to Classify High Risk MDS

- Based on blast percentage in the bone marrow, number of low blood counts, and the chromosome changes in the bone marrow

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Overall Score</th>
<th>Median Survival (yrs)</th>
<th>25% AML progression (yrs) w/o therapy</th>
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<tr>
<td>Low</td>
<td>0</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>INT-1</td>
<td>0.5 - 1.0</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>INT-2</td>
<td>1.5 - 2.0</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>High</td>
<td>≥ 2.5</td>
<td>0.4</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Important to remember that these outcomes are based on UNTREATED patients
WPSS to Classify High Risk MDS

- Based on WHO based morphology classification + bone marrow chromosome changes + red cell transfusion needs

"Why is all this Classification and Definition in MDS needed?"

- It is NOT meant to scare you

- Important to remember that these scores and survival predictions (IPSS and WPSS) were developed based on patients who did NOT receive treatment

- The scores help the doctors decide what the best approach to therapy:
  - When to treat
  - What therapy to consider
Treatment Options for Higher Risk MDS

- Treatment to “Control” MDS:
  - Not curative but can hopefully improve quality of life and alter the risk of progression to acute leukemia
  - Hypomethylating Agents:
    - Azacitidine: FDA Approved May 2004
    - Decitabine: FDA Approved May 2006
  - Clinical Trials
- Treatment to “Cure” MDS:
  - Stem Cell Transplant
Azacitidine and Decitabine:
General Information

- First “disease modifying” non-transplant therapies to gain approval for therapy for MDS patients
  - Improve quality of life
  - Change chance of progression to acute leukemia

- “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 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
What to Expect: Decitabine

- **Standard Treatment Cycle**: Daily Injections for 5 Days in a row repeated every 4 weeks
  - Only given IV

- **Common Side Effects**:
  - Low Blood Counts
  - Gastrointestinal changes
  - Skin changes
  - Fatigue
  - Headache
  - Some blood chemistry changes
  - Cough

What to Expect with Decitabine: *Response Rates*

- Overall response rates similar to azacitidine: 40-60% but complete remission rates seem slightly higher

- Quality of life improved in those that respond

- Possible improved overall survival
Azacitidine and Decitabine: 

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: continue monthly therapy as long as benefit and minimal toxicity
  - Not a “cure”
Intensive Chemotherapy

- Acute Leukemia Type Inpatient chemotherapy: Standard Regimen = 7+3
  - Typically used only for patients with very high risk MDS
    - Those with a very high blast percentage nearing the acute leukemia threshold
    - Those with MDS that seems to be progressing quickly
    - Those whose goal of therapy is a cure with planned stem cell transplant in the future and attempt to minimize delay in moving ahead to transplant

Intensive Chemotherapy: Summary

- Benefits:
  - Works quicker
  - Decreases time of low counts
    - Possibly decreases time of transfusion needs and infection risk
  - May give higher complete remission rates

- Drawbacks:
  - 4 week hospital stay
  - Higher risk for up front side effects and organ toxicity since more aggressive chemotherapy
“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 so that normal blood cells are not made and transfusions are needed.
“What is a Stem Cell Transplant?”

- Two Step Process:
  - “Conditioning:” Using chemotherapy +/- radiation to “get rid” of the MDS 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 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 cells that the chemotherapy couldn’t
“Why don’t we do stem cell transplants for everyone?”

- Not everyone has a donor

- 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, the MDS chromosome changes, and the status of the MDS at transplant

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

- The potential risk of transplant is much higher than other therapies:
  - Side Effects:
    - Infection risk is substantial the first year or so after transplant
    - Organ damage from chemo, anti-rejection medications, or antibiotics
    - Graft Versus Host Disease: The new immune system attacking the patient (not just the MDS)
  - Life threatening complications: risk of dying ranges from 15-30% depending on the type of transplant
“If the risks are that high, why do we consider transplant?”

- We balance the risk of the disease (MDS) with the risk of the treatment (transplant):
  - If the risk of a life altering complication due to MDS is higher then the risk from the transplant, then it makes sense to consider the transplant
  - How do we make that risk assessment?
    - Back to the IPSS and WPSS that we discussed in the beginning. That is why these risk scoring systems are so important!

### Treatment Decision-Making

- **Transplant Candidate?**
  - **Yes**
    - INT-2/High WPSS ≥ 2
      - +/- Pre-Transplant Treatment: Azacitidine Decitabine Intense Chemo
        - Transplant
  - **Low/INT-1 WPSS < 2**
    - Options: Growth Factors Lenalidomide Azacitidine Clinical Trials
      - Progression?
  - **INT-2/High WPSS ≥ 2**
    - Azacitidine Decitabine Clinical Trials
“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

What Is New on The Horizon For MDS?
Overview

- Review Current and Future Diagnostic and Prognostic Models for MDS
- Review concept of “epigenetics” in MDS
- Review new treatments in development for MDS

Current Ways to Diagnose MDS

- Current diagnosis focuses on:
  - Morphology (what the cells look like under the microscope)
  - Flow Cytometry: specialized lab test that identifies “blasts” by surface flags (which helps to categorize the MDS)
  - Chromosome Analysis of the bone marrow: to predict prognostic group
Current Ways to Predict Prognosis in MDS

- Current Prognostic Scoring Systems:
  - IPSS
  - WPSS

- Benefits of these systems:
  - Easy point calculations to put patients in risk groups and help predict prognosis
  - Help guide treatment decisions

- Drawbacks:
  - Underestimate impact of specific MDS features on prognosis
  - Developed based on untreated patients with MDS that developed “out of the blue”

Future Predictive Tools

- Both the WPSS and the IPSS scoring systems are being revised to include:
  - More detailed risk scores based on the MDS chromosome changes
  - More detailed risk scores based on the low blood counts
  - Expanded risk groups

- Specialized gene testing to predict prognosis

- The goal of these changes are to improve prognosis prediction to improve treatment decision making
Epigenetic Basics

General Info:

- All cells are made of DNA that is the “blue-print” for the development of the cell. The DNA basically tells the cell what to do

- Processes called “methylation” and “histone acetylation” that change the surface “flags” on the DNA and change the message that the DNA gives to the cell

Epigenetic Basics

- In MDS: Increased methylation and altered histone acetylation lead to:
  - Funny looking (dysplastic) cells that don’t “grow up” or work correctly

- Many of the treatments we have for MDS target methylation and histone acetylation to try to “fix” the problem and make the cells grow up and function correctly
  - Azacitidine, Decitabine, etc
New Treatments

Oral Azacitidine

- Early in Evaluation
- Current studies have evaluated:
  - Safety
  - Side Effects:
    - Most common were GI side effects, headache, fatigue, peripheral edema
  - Dosing: Schedule used within the studies similar to standard doses
  - Response:
    - Overall response:
      - Untreated Patients: 73%
      - Previously treated Patients: 35%
Combination Azacitidine and Lenalidomide

- Early Stage Studies looking at different dose combinations to find the safest effective dose
  - Treatment Schedule: Various dose schedules repeated every 4 weeks
  - Side Effects: GI issues, injection site reaction, itching, rash, fatigue, dizziness, fever
  - Response: 67% responded to therapy (with a high percentage of complete remissions)

Clofarabine

- Studied in both an oral and IV form
- Many doses investigated for both routes
- Side Effects: nausea, skin rash, liver test changes, fatigue, count suppression, infections
- Responses: Overall responses 30-40%
  - Improved survival in those responders
- The best dose and schedule still to be determined
Ezatiostat

- New oral and IV drug that attempts to increase growth and maturation of blood cells and kill blasts
- Doses: A variety of doses have been studied
- Side Effects: Nausea, vomiting, diarrhea, minimal blood count abnormalities
- Responses:
  - Primary responses were mostly improved red blood cell counts (22%)
  - Patients treated with prior azacitidine/decitabine had lower responses

Platelet Stimulants: Romiplostim

- Romiplostim = IV or SQ platelet growth factor studied initially in patients with ITP (immune attack on platelets)
- MDS Studies focused on lower risk patients with low platelet counts not getting other therapy
- Side Effects: Most common side effects were fatigue and headache
  - Infrequent finding of progression to acute leukemia
- Response rates range from 40-70%
- Studies are early and long term toxicities unknown
  - Additional research in MDS important to determine long term safety and responses
Platelet Stimulants: Eltrombopag

- Eltrombopag: an oral platelet growth factor studied initially in ITP
  - Few studies in MDS
  - Current national study underway
  - Preliminary studies suggest some response in MDS
    - Further study on long term impact needed

Clinical Trials

- Hundreds of clinical trials combining standard agents and investigating new agents are underway around the world
  - These trials push medical science forward and enable new treatments to become standard for MDS
Final Thoughts

- Higher risk MDS is an aggressive blood disorder that requires close monitoring and therapy to improve survival and quality of life.

- Treatment decisions can be challenging due to the variability of disease, patient age and other medical problems, insurance issues (until recently), and consideration of treatment goals.

Final Thoughts

- Goal of Cure:
  - Possible chemotherapy to decrease the burden of MDS
  - Stem Cell Transplant

- Goal of Disease control:
  - Hypomethylating agents (Azacitidine or Decitabine)
  - CLINICAL TRIALS: Crucial to improving our knowledge about MDS and developing better and less toxic treatments

- Good treatment exists and close monitoring and specialized care can improve patient experience and survival.
Final Thoughts…

- In order to best treat patients we need to:
  - Better describe patient prognosis
  - Better predict which treatments patients will respond to
  - Develop more personalized therapies that maximize response and minimize side effects

Final Thoughts…

- Whether or not we will find therapies other than transplant that will cure patients is unknown
  - However, if we can develop additional well tolerated chemotherapy combinations that control MDS and alleviate the symptoms of disease with a good quality of life, then we have been successful