Treating Patients with Higher Risk Myelodysplastic Syndromes

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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”

“How Do We Classify MDS?”
- FAB 1970-1980’s
-IPSS 1997
-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)</th>
</tr>
</thead>
<tbody>
<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>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 2.0</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

Hypomethylating Agents
- Azacitidine
- Decitabine
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
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

Stem Cell Transplant

Potentially Curative Therapy

“First things first: What is a Stem Cell?”

- Hematopoietic (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

“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

“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
“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 ever consider transplant?”

- We balance the risk of the disease (MDS) with the risk of the treatment (transplant):
  - If MDS Risk >>> Transplant Risk 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
  - No

  - INT-2/High WPSS ≥ 2
  - Low/INT-1 WPSS < 2

- Pre-Transplant: Azacitidine, Decitabine, Intense Chemo
- Options: Growth Factors, Lenalidomide, Azacitidine, Clinical Trials
- Progression?

“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 Higher Risk MDS?
Updated Prognostic Scoring System

- Revised IPSS (IPSS-R)
  - Expands cytogenetic Groups
  - Expands impact of degree of low blood counts
  - Expands prognostic scoring groups further
    - May help to better inform treatment decisions

Combination Therapy

- Numerous published studies combining:
  - Azacitidine + Lenalidomide
  - Azacitidine/Decitabine + HDACi's
    - Aza + MS-275
    - Aza + Vorinostat
  - Clofarabine +/- Cytarabine
  - Other Novel combinations

Clofarabine

- Aza 75 mg/m2 Days 1-5 + Lenalidomide 10 mg Days 1-21 of a 28 day cycle
- 36 patients (18 phase I and 18 phase II)
  - INT-1 (n=5), INT-2 (n=20), and High (n=11)
  - 31% previously treated with therapy beyond growth factors
- **Overall Response Rate = 72%**
  - Complete Remission: 44%
  - Hematologic Remission: 28%
    - (Note: ORR in AZA-001 49% with CR rate 17%)
- Median Survival for entire group 13.6 months
  - Survival for responders: 37.5 months

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

Summary

- 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
Summary

- 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

Questions