What is MDS?

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Disclosures

- Research funding from Gilead and Protagonist
Goals

• Review the incidence of MDS

• Understand how the bone marrow works

• Describe how MDS changes bone marrow function
What is MDS?

- MDS is a heterogeneous group of blood cancers that are characterized by low blood counts.
- In MDS, the bone marrow fails to make normal, healthy blood cells.
- ~35-40% of patients with MDS will progress to having acute myeloid leukemia (AML).
How Common is MDS?


~4.7/100,000
Does MDS Become More Common as We Age?

What is the Bone Marrow?

Red Blood Cells - Carry oxygen
White Blood Cells - Prevent/fight infection
Platelets - Clot blood and prevent bleeding
What Happens to the Bone Marrow in MDS?

Damage to the factory cells and the bone marrow environment creates defects in normal blood cell development (dysplastic changes and cytopenias) and an overproduction of immature cells (blasts).

Adapted from: Stem cell basics, National Institute of Health Stem Cells information website.
What Happens When Blood Counts are Low?

- **Anemia (Low hemoglobin)**
  - Fatigue
  - Shortness of breath
  - Pale eyes or skin
  - Abnormal heartbeat

- **Leukopenia/neutropenia (Low white blood cells)**
  - Fever
  - Infections

- **Thrombocytopenia (Low platelets)**
  - Bleeding
  - Bruising
  - Rash
How Is MDS Diagnosed?

• Complete blood count (CBC)
• Bone marrow aspirate and biopsy
How is MDS Classified?

2022 WHO Classification

2022 WHO Classification

2022 WHO Classification

History
Chemotherapy ± radiotherapy

Myelodysplastic Neoplasm

Myelodysplastic Neoplasm

Myelodysplastic Neoplasm

Myelodysplastic Neoplasm

History

Myelodysplastic neoplasm post cytotoxic therapy

MDS with defining genetic abnormalities
MDS with low blasts and isolated 5q deletion
MDS with low blasts and SF3B1 mutation
MDS with multi-hit TP53 alterations

MDS defined by morphology
MDS with low blasts
MDS, hypoplastic
MDS with increased blasts*

*Exclude AML with defining genetic abnormalities as relevant

How Do We Determine the Prognosis for MDS?
How Do We Determine the Prognosis for MDS?

STRATIFICATION RESULTS

- IPSS-M Score: 2.33 (VERY HIGH)
- IPSS-R Score: 8.00 (VERY HIGH)
- IPSS-R Score (Age-adjusted): 8.05 (VERY HIGH)

ENDPOINTS

- Leukemia-Free Survival (IPSS-M): 0.76 years (median)
- Overall Survival (IPSS-M): 1 year (median)
- NLR Transformation (IPSS-M): 28.2% by 1 year

Risk Stratification

Clinical Outcomes

- Hazard Ratio
- Graph
- Table

Hazard ratio for risk of AP/C or death from any cause compared to the average patient.


Study supported by the IPSS Foundation.
Thank you!
How do we treat MDS?

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Professor of Medical Oncology
Director, Leukemia Program
Medical Director, Cancer Clinical Research Operations
Sidney Kimmel Cancer Center
Thomas Jefferson University Hospital
Philadelphia, PA
Treatment Paradigm

- Define the risk
- Defining the treatment goals
- The only curative treatment for MDS is allogeneic stem cell transplant

Management of Lower- MDS

Treatment Goals:

• Improving cytopenias
• Decreasing transfusion burden
• Improving QOL
Management of Low-Risk MDS (IPSS ≤1 or R-IPSS ≤3.5 points)

- Minimal symptoms
  - No transfusion needs
  - Observation
  - Surveillance

- Symptomatic anemia and/or Hb <19 g/dL
  - sEPO >500 U/L
  - sEPO ≤500 U/L
    - ESA +/- G-CSF
    - Unlikely to respond to ESA
    - Failure or loss of response

- Failure or loss of response
  - del(5q)
  - non-del(5q)

- Transfusions and/or TPO-RA**
  - No response or loss of response
  - Clinical trial HMA

- MDS-RS and/or SF3B1 mutation
  - Luspatercept
  - IST*

- Hypoplastic MDS
  - Others

- Clinical trial
  - Lenalidomide +/- ESA
  - HMA
  - Allogeneic HCT

Lower-Risk without Ring Sideroblasts and no SF3B1: First Line

Epo < 500
- Luspatercept
- ESA/Epo (red cell growth factor)
- If no response can increase dose or add white cell growth factor

Epo > 500
- Luspatercept ????
- Hypomethylating agents (azacitadine, decitabine, oral decitabine)

If platelets are the problem

Oral or subcutaneous platelet growth factors (eltrombopag, romiplostim)
Lower-Risk without Ring Sideroblasts and no SF3B1: Second Line and beyond

Epo < 500
- ESA (red cell growth factor)
- If no response can increase dose or add white cell growth factor
- Luspatercept

Epo > 500
- Received hypomethylating agents:
  - Clinical trial
  - Transplant
  - Supportive care
- Haven’t received hypomethylating agents:
  - Hypomethylating agent
  - Lenalidomide
Lower-Risk WITH Ring Sideroblasts and/or SF3B1: First Line

Epo < 500
- Luspatercept
- ESA (red cell growth factor)
- If no response can increase dose or add white cell growth factor

Epo > 500
- Luspatercept

If platelets are the problem

Oral or subcutaneous platelet growth factors (eltrombopag, romiplostim)
Lower-Risk WITH Ring Sideroblasts and/or SF3B1: Second Line and beyond

- Luspatercept (if the first line was growth factors)
- Growth factors if the first line was luspatercept
- Lenalidomide
- Hypomethylating agent
  - Clinical trial
  - Transplant
  - Supportive care
Lower-Risk - Deletion (5q-) syndrome

- Isolated cytogenetic abnormality
- Less than 5% blasts
- Anemia
- Elevated platelets

- First line: Lenalidomide
- Second line and beyond:
  - Growth factor if eligible
  - Hypomethylating agents
  - Clinical Trials
  - Supportive Care
Management of High-Risk MDS (IPSS ≥1.5 or R-IPSS ≥4 points)

Transplant eligible
- ≥10% blasts
  - Bridge therapy (e.g. HMA or ICT)
  - HCT
  - Relapse
    - Clinical trial
      - HMA
      - Targeted therapy
      - Second HCT
      - DLI
- <10% blasts
  - HCT

Transplant ineligible
- HMA until disease progression
  - Failure
    - Clinical trial
      - Targeted therapy
      - Chemotherapy
Higher-Risk: First Line

Transplant candidate (or not)

• Hypomethylating agents (azacitadine, decitabine, oral decitabine)
  • 40-50% respond
  • Median duration of response is about 1 year
  • Leukemia-like therapy including chemotherapy if blast count is higher than 10%
Higher-Risk: Second Line and beyond

Transplant candidate (or not)
• Clinical trial
• Leukemia-type therapy including chemotherapy
• Targeted therapy
• Supportive care
• Palliative care
Thank you!
MDS Research

Gina Keiffer, MD
Assistant Professor of Medical Oncology
Sidney Kimmel Cancer Center
Thomas Jefferson University Hospital
Philadelphia, PA
Why do we need research in MDS?

- MDS is a complex spectrum of disease with variable cytopenias and risk of progression to AML and treatment must be individualized.

- Lower-risk patients may struggle with transfusion burden and debilitating symptoms for which treatment options are limited.

- Higher-risk patients may progress quickly to AML or may not be candidates for stem cell transplant.
  - Median survival with standard of care azacytidine is only 12 months.

- Outcomes are poor after failure of initial treatment.
Why is MDS so complicated to treat?

Drug approvals in MDS

Research Process

Clinical Trials

- **Preclinical**: Drug Approved for Testing in Humans (20-80 Participants)
- **Phase 1**: 20-80 Participants
- **Phase 2**: 100-300 Participants
- **Phase 3**: 1,000-3,000 Participants
- **FDA Review**: To Confirm Safety and Effectiveness
- **Phase 4**: 1,000+ Participants

Drug Submitted for FDA Approval

Drug Approved
Ongoing Research in MDS
(Some) Research Questions in MDS

• How do we decrease burden of cytopenias in lower-risk MDS?
• Does starting treatment before transfusion-dependence develops lessen, delay or prevent transfusion burden?
• How should available therapies be combined in the treatment of higher-risk MDS?
  • Who benefits from combination treatment?
  • What is the optimal dosing regimen?
• What is the optimal all-oral treatment?
# Studies with Venetoclax in HR-MDS

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Population</th>
<th>Median PFS</th>
<th>Median OS (Median Follow UP)</th>
<th>ORR</th>
<th>CR</th>
<th>Patients Enrolled</th>
<th>Study Phase</th>
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</thead>
<tbody>
<tr>
<td>Garcia JS et al.</td>
<td>Venetoclax + AZA</td>
<td>Rx-naive HR-MDS</td>
<td>-</td>
<td>27.5</td>
<td>77%</td>
<td>42%</td>
<td>78</td>
<td>Ib</td>
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<tr>
<td>Ball et al.</td>
<td>Venetoclax + HM</td>
<td>Rx-naive and R/R MDS</td>
<td>15.4 months</td>
<td>19.5 (7.6)</td>
<td>59%</td>
<td>14%</td>
<td>44</td>
<td>Ib</td>
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<tr>
<td>Zeidan AM et al.</td>
<td>Venetoclax + AZA</td>
<td>R/R MDS</td>
<td>8.6 months</td>
<td>12.2 (21.2)</td>
<td>39%</td>
<td>7%</td>
<td>37</td>
<td>Ib</td>
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</tbody>
</table>

Azacitidine + Venetoclax

- Phase Ib/II single-arm with Aza + Venetoclax for treatment-naive high-risk MDS
  - Aza 75 mg/m² days 1-7 every 28 days
  - Ven 100-400 mg days 1-14 every 28 days

- Primary endpoint: Safety and recommended phase II dose

- Median OS: NR (16.1 mos - NR)
- Median PFS: 17.5 mos

## Select Enrolling Studies in Lower-Risk MDS

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>NCT#</th>
<th>Population</th>
<th>Phase</th>
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</thead>
<tbody>
<tr>
<td>Oral AZA + BSC vs placebo</td>
<td>05469737</td>
<td>Lower-risk MDS</td>
<td>III</td>
</tr>
<tr>
<td>Luspatercept</td>
<td>05949684</td>
<td>Non-transfusion dependent</td>
<td>III</td>
</tr>
<tr>
<td>Eltrombopag</td>
<td>04797000</td>
<td>Platelet-transfusion dependent</td>
<td>II</td>
</tr>
<tr>
<td>Canakinumab (anti-IL-1b) + darbopoietin</td>
<td>04798339</td>
<td>RBC-transfusion dependent who failed ESA</td>
<td>IIIb/II</td>
</tr>
<tr>
<td>Hetrombopag</td>
<td>05392647</td>
<td>With thrombocytopenia</td>
<td>II</td>
</tr>
<tr>
<td>Luspatercept + lenalidomide</td>
<td>04539236</td>
<td>Non-5q- MDS</td>
<td>I/II</td>
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</tbody>
</table>
## Select Enrolling Studies in Higher-Risk MDS

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<th>NCT#</th>
<th>Population</th>
<th>Phase</th>
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</thead>
<tbody>
<tr>
<td>Lemzoparlimab (anti-CD47) + AZA vs AZA</td>
<td>05709093</td>
<td>Treatment-naïve</td>
<td>III</td>
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<tr>
<td>Oral AZA vs placebo</td>
<td>04173533</td>
<td>Maintenance tx post-alloSCT</td>
<td>III</td>
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<tr>
<td>AZA + cedazuridine</td>
<td>04256317</td>
<td>MDS, AML, CMML</td>
<td>III</td>
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<tr>
<td>Orca-T (engineered T cells)</td>
<td>05316701</td>
<td>AlloSCT recipients with hematologic malignancies</td>
<td>III</td>
</tr>
<tr>
<td>Oral AZA + venetoclax</td>
<td>05782127</td>
<td>Treatment-naïve</td>
<td>I/II</td>
</tr>
</tbody>
</table>

Clinicaltrials.gov
Sometimes research comes with disappointments...

Press Releases

July 21, 2023

Gilead To Discontinue Phase 3 ENHANCE Study of Magrolimab Plus Azacitidine in Higher-Risk MDS

FOSTER CITY, Calif.--(BUSINESS WIRE)-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced that the Phase 3 ENHANCE study in higher-risk myelodysplastic syndromes (MDS) has been discontinued due to futility based on a planned analysis. The safety data seen in this study is consistent with the known magrolimab profile and adverse events that are typical in this patient population. Gilead recommends discontinuing treatment with magrolimab in patients with MDS. Magrolimab is a potential first-in-class, anti-CD47 immunotherapy with a clinical development program spanning ten potential indications including ongoing trials in solid tumors and two pivotal trials: ENHANCE-2 study in acute myeloid leukemia (AML) with TP53 mutations and ENHANCE-3 in first-line, unfit AML.
Interested in Participating in MDS Research?
MDS Research Resources

• Jefferson Resources:
  • Visit: research.jefferson.edu
  • Email: JCRI@Jefferson.edu, askphase1@Jefferson.edu

• MDS Foundation:
  • Search clinical trials: mds-foundation.org/clinical-trials

• Leukemia and Lymphoma Society Clinical Trial Support Center: lls.org
  • One-on-One assistance with LLS Clinical Trial Nurse Navigator

• National Clinical Trials Database: clinicaltrials.gov
Thank you!
Overview of Stem Cell Transplant

Xia Bi, MD
Assistant Professor
Department of Medical Oncology
Division of Hematologic Malignancy and Stem Cell Transplantation
Sidney Kimmel Cancer Center, Thomas Jefferson University
What are Stem Cells?

- Stem cell
  - Bone marrow
  - White blood cells (lymphocytes, neutrophils and other types)
  - Red blood cells (erythrocytes)
  - Platelets (thrombocytes)
How aHSCT Works

STEP 1
Pre-treatment releases blood stem cells from bone marrow into the bloodstream.

STEP 2
Blood stem cells are collected from the bloodstream.

STEP 3
Blood stem cells are frozen in the laboratory.

STEP 4
Undergo chemotherapy to suppress or partially suppress the immune system.

STEP 5
Blood stem cells are thawed and infused back into the body through the vein.

STEP 6
Continue medical treatment as the immune system rebuilds.

Image originally created by MS Australia: msaustralia.org.au
Types of stem cell transplants

- Autologous Transplant
  - Utilizes the patient’s own stem cells

- Allogeneic Transplant
  - Utilizes someone else’s stem cells donated by:
    - Family members - siblings, parents, children
    - Unrelated donors from the National or International Marrow Donor Program (NMDP)
    - Umbilical cord donations

- Syngeneic Transplant
  - Utilizes an identical twin
Criteria for stem cell transplant

Age is NOT a barrier!
Donor evaluation

- Related donors - he/she will work with a specialized doctor and coordinator to ensure safe and individualized care
- Unrelated donors - institution will work with the National Marrow Donor Program (Be The Match)
Hospital stay

- Allogeneic ~ 4-5 weeks depending on the conditioning regimen and recovery process
- Closed BMT unit
- Physicians, midlevel practitioners, BMT pharmacist, RNs, etc
Supportive care

• Blood transfusions
• Antibiotics, antivirals, antifungals - many of these will continue outpatient for some time
• Fluid & electrolyte replacement
• Additional side effect management
Discharge & beyond

- Criteria for discharge
  - 1. Blood counts
  - 2. Nutrition
  - 3. Mobility
- Medications
- Caretaker
- Follow up
Sidney Kimmel Cancer Center

At Sidney Kimmel Cancer Center, our approach is called Cancer Care 360. It’s a comprehensive circle of care—including research, treatment and support — built around you.