Treatment Options for Myelodysplastic Syndromes

Scott R Solomon, MD
Blood and Marrow Transplant Program at Northside Hospital
Overview

• Describe the background & pathophysiology of MDS

• Review the treatment goals & current treatment options for low & high-risk MDS

• Describe adjunctive/supportive therapies that complement the overall treatment plan
Definition

- A heterogenous group of **clonal stem cell** disorders
- Characterized by dysfunctional hematopoietic progenitor cells
- Resulting in low blood count
Background

- 1930s-first described as a pre-leukemic condition
- 1976-considered as a separate disease entity
- ~15,000 new cases/year in US (adults)
Disease Characteristics

• Typically cellular to hypercellular marrows
• Dysplastic hematopoiesis in ≥ 1 cell line
  – Erythroid = Anemia
  – Granulocytes = Leukopenia
  – Megakaryocytes = Thrombocytopenia
• Ineffective hematopoiesis:
  – failure of differentiation
  – increased cell death or apoptosis
Etiology

- Unknown in >80% of patients
- Older age
- Male gender
- Secondary MDS
  - Ionizing radiation
  - Chemotherapy
  - Industrial & agricultural chemicals (benzene)
Age-related Incidence of MDS

Age-specific incidence rates (per 100,000)

- Less than 50: 0.5
- 50-59: 5.3
- 60-69: 15
- 70-79: 49
- 80 and over: 89

Age in 5-year blocks

Differential Diagnosis

- B12/folate deficiency
- Drug-induced or recent cytotoxic therapy
- HIV
- Anemia of chronic diseases
- Autoimmune cytopenias
- Chronic liver disease & excess alcohol intake
- AML (M7), aplastic anemia, myelofibrosis, and PNH
MDS: Diagnostic Evaluation

- Peripheral blood counts & reticulocyte count
- Bone marrow biopsy & aspiration
  - Bone marrow blasts%
  - Cytogenetics
  - Iron stain
  - Reticulin stain
- Additional tests (iron saturation, ferritin, EPO, HLA-DR15, HLA typing)
Classifications

• French American British (FAB), 1982
• World Health Organization (WHO), 2001

Prognostic Scoring

• International Prognostic Scoring System (IPSS), 1997
• World Prognostic Scoring System (WPSS), 2007
<table>
<thead>
<tr>
<th>FAB</th>
<th>WHO</th>
<th>Dysplasia(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>5q- Syndrome</td>
<td>Erythroid</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>Erythroid</td>
</tr>
<tr>
<td></td>
<td>RCMD</td>
<td>2-3 lineages</td>
</tr>
<tr>
<td></td>
<td>MDS-U</td>
<td>1 lineages</td>
</tr>
<tr>
<td>RARS</td>
<td>RARS</td>
<td>Erythroid</td>
</tr>
<tr>
<td></td>
<td>RCMD-RS</td>
<td>2-3 lineages</td>
</tr>
<tr>
<td>RAEB</td>
<td>RAEB-1 (5-9%)</td>
<td>1-3 lineages</td>
</tr>
<tr>
<td>(Blasts 5-19%)</td>
<td>RAEB-2 (10-19%)</td>
<td>1-3 lineages</td>
</tr>
<tr>
<td>RAEB-T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Blasts ≥20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMMoL</td>
<td>CMMoL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(if WBC &lt; 13,000u/l)</td>
<td></td>
</tr>
</tbody>
</table>

Relative % of Various Cytogenetic Abnormalities in De Novo MDS

- Normal: 40%
- Abn5: 8%
- Abn7: 8%
- Abn5&7: 15%
- Y: 7%
- Abn17p: 7%
- Del(20q): 4%
- 11(q23): 1%
- 8+: 10%
5q- syndrome

- Myelodysplastic syndrome associated with isolated del (5q) chromosome
- < 5% Blasts in marrow and blood
- Predominantly middle-aged to older women
- Severe Refractory Anemia (Macrocytic)
- Hypercellular marrow with abnormal megas
# International Prognostic Scoring System (IPSS)

All 3 prognostic variables required to generate IPSS score

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow blasts (%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
</tr>
<tr>
<td>Number of cytopenias**</td>
<td>0/1</td>
</tr>
</tbody>
</table>

*Good = Normal, -Y, del(5q), del(20q)

*Intermediate (Int)= Other karyotypic abnormalities

*Poor = Complex (≥ 3 abnormalities) or chromosome 7 abnormalities

**Hgb <10 g/dL; ANC <1800/μL; Platelets <100,000/μL
Survival & Transformation to AML by IPSS Score*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low</th>
<th>Int-1</th>
<th>Int-2</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>0</td>
<td>0.5-1.0</td>
<td>1.5-2.0</td>
<td>≥ 2.5</td>
</tr>
<tr>
<td>Median Survival, years</td>
<td>5.7</td>
<td>3.5</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Median AML Transformation, years</td>
<td>9.4</td>
<td>3.3</td>
<td>1.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*From diagnosis in untreated patients.
# Survival: MDS vs. Lung Cancer

<table>
<thead>
<tr>
<th>IPSS Score</th>
<th>Risk Group</th>
<th>Median Survival (Yrs)</th>
<th>Stage</th>
<th>Median Survival (Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
<td>Ia</td>
<td>8</td>
</tr>
<tr>
<td>0.5-1</td>
<td>Int-1</td>
<td>3.5</td>
<td>Ila</td>
<td>5.4</td>
</tr>
<tr>
<td>1.5-2</td>
<td>Int-2</td>
<td>1.2</td>
<td>Illa</td>
<td>2.4</td>
</tr>
<tr>
<td>&gt;2</td>
<td>High</td>
<td>0.4</td>
<td>IV</td>
<td>1.2</td>
</tr>
</tbody>
</table>

The survival of MDS Int-2 patients is similar to survival of patients with stage 4 lung cancer.
**WHO Prognostic Scoring System (WPSS)**

<table>
<thead>
<tr>
<th>WHO Subtype</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>RA, RARS, 5q</td>
<td></td>
</tr>
<tr>
<td>RCMD, RCMD-RS</td>
<td></td>
</tr>
<tr>
<td>RAEB-I</td>
<td></td>
</tr>
<tr>
<td>RAEB-II</td>
<td></td>
</tr>
</tbody>
</table>

| Transfusion Requirement| None   | Regular*|       |       |
|                       |        |         | _     | _     |

| IPSS Cytogenetic Risk | Good   | Int.    | Poor  | _     |

*Defined as ≥ 1 U pRBC q 8 wk
WPSS WHO-Based Prognostic Scoring System for Predicting Survival in MDS

<table>
<thead>
<tr>
<th>WPSS Risk Group</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>3-4</td>
</tr>
<tr>
<td>Very High</td>
<td>5-6</td>
</tr>
</tbody>
</table>

Survival Based on WPSS

Low Risk MDS - Treatment Goals

• Definition
  – IPSS low or intermediate-1

• Goals
  – Delay disease progression
  – Prolong survival
  – Improve blood cell deficiencies
  – Improve quality of life
High Risk MDS - Treatment Goals

- **Definition**
  - IPSS Intermediate-2/High

- **Goals**
  - Possible cure of disease
  - Delay AML
  - Prolong survival
Supportive Care Components

- Transfusions (Leukocyte-depleted RBCs, platelets)
- Growth Factors
- Iron Chelation
- Antibiotics
Erythropoietic Stimulating Agents (ESA)

- Often initial therapy
  - low-risk
  - transfusion-dependent patients

- Features that predict response:
  - endogenous epo < 500 U/ml
  - low transfusion requirement (<2U/month)
  - bone marrow blasts < 10%
Erythropoietic Stimulating Agents (ESA) +/- G-CSF: Dosing

• Epoetin 20,000 U sq 3x / week or
• Epoetin 60,000 U sq weekly or
• Darbepoetin 300 mcg sq weekly
• If no response after 6-week trial, add G-CSF 100 mcg sq 3x/week to maintain neutrophil count 5 – 10 x 10^9/l
• Discontinue if no response after 12 weeks

Predictive Model for Response to Treatment with rhuEPO + G-CSF

RA, RARS, RAEB

Score > +1

Response Probability

Good
(74%, n=34)

Score = -1- +1

Intermediate
(23%, n=31)

Score < -1

Poor
(7%, n=29)

Treatment Response Criteria

CR
Stable Hemoglobin
> 11.5 g/dl

PR
Increase in Hb with
>1.5g/dl or total stop in RBC transfusions

Treatment Response Score

<table>
<thead>
<tr>
<th>S-EPO u/l</th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>100-500</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>&gt;500</td>
<td>-3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transf U RBC/ m</th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 units/m</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>≥2 units/m</td>
<td>-2</td>
<td></td>
</tr>
</tbody>
</table>

Iron Chelation

- 1 PRBC transfusion = ~ 200mg iron
- Chronic transfusions (20-30 U) → iron overload
- Iron overload → oxygen free radicals
- Oxygen free radicals → cardiac, liver, pancreas toxicity
- Possible hematopoietic toxicity?
Iron Chelation and Survival

- OS significantly better for pts who received iron chelation therapy
- Results consistent across all subgroups analyzed (IPSS low and intermediate-1, sex, age)

Median survival: 63 months (whole group)
115 vs 51 months ($P < .0001$)
Iron Chelation Considerations

• Who can benefit?
  – Low-risk, intermediate-1 risk
  – Life expectancy > 1-2 years
  – Continued need for RBC transfusions
  – Existent cardiac or hepatic dysfunction

• Monitoring:
  – Ferritin levels (goal < 1000 mcg/L)

• Preferred route of therapy
Iron Chelation Options

Deferoxamine (Desferal®)

Route: SQ

t ½: 0.5 hours

Dosing: Infused over 8-12 hrs
5-7 nights/week

Deferasirox (Exjade®)

Route: PO

t ½: 12-16 hours

Dosing: Dissolved in solution, taken daily
Prevention & Treatment of Infections

Prevention

Prophylactic antibiotics ➔ No routine prophylaxis

Patient education ➔ know your nadir

report a fever

recognize signs of infection

avoid illness, crowds

update vaccinations

Treatment ➔ Febrile neutropenia guidelines

www.nccn.org/MDS v1..2008
Pharmacotherapy In MDS

- Azacitidine
- Decitabine
- Lenalidomide
- Anti-thymocyte Globulin (ATG)
Indications for Azacitidine for Injection (Vidaza®)

• First FDA-approved treatment for MDS
• Azacitidine is indicated for treatment of patients with all MDS subtypes:*
  – RA or RARS if accompanied by neutropenia or thrombocytopenia or requiring transfusions
  – RAEB
  – RAEB-T
  – CMMoL (chronic myelomonocytic leukemia)

*According to the FAB (French, American, British) Classification System. VIDAZA full prescribing information
Phase III Clinical Trial Design: 5-Azacitididine (Azacitididine)

• Trial Design: A randomized, cross over, Phase III

• Subjects: Treatment-naïve RA, RARS, RAEB/T, CMMoL

• Arms: Azacitididine (75 mg/m² SQ x 7 days q 28 days) plus Best Supportive Care versus Best Supportive Care (BSC) Alone

• Primary endpoints: CALGB Response rate

Azacitidine Survival Study

Survival Study Design

Azacitidine 75 mg/m\(^2\) x 7 days
Every 28 days

Standard of Care Options consist of:
1. Best Supportive Care
2. Low Dose Ara-C
3. Standard Chemotherapy
Overall Survival: Azacitidine vs CCR

ITT Population

Log-Rank  \( p=0.0001 \)

HR = 0.58 [95% CI: 0.43, 0.77]

Deaths: AZA = 82, CCR = 113

Difference: 9.4 months

Time (months) from Randomization

Proportion Surviving

- AZA
- CCR

15 months

50.8%

24.4 months

26.2%
Indications for Decitabine (Dacogen™)

- Decitabine is indicated for treatment of patients with MDS including:
  - Previously treated & untreated, *de novo* & secondary MDS of all FAB subtypes (RA, RARS, RAEB, RAEB-t, CMMoL)
  - Intermediate-1, intermediate-2, & high-risk IPSS groups
Clinical Trial Data: Decitabine

- **Trial Design:** An open-label, multicenter, 1:1 randomized study
- **Subjects:** De novo or secondary MDS IPSS Int-1, Int-2 and high-risk MDS
- **Arms:** Decitabine (15 mg/m$^2$ IV q8 hrs x 3 days q6 weeks) versus Best Supportive Care
- **Primary endpoints:** IWG Response rate, Time to AML/death

*Cancer* 2006; 106: 1794.
## Comparison of Decitabine & Azacitididine Phase 3 Trials

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Decitabine</th>
<th>Azacitididine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response Rates</strong> <em>(CR + PR)</em></td>
<td>17% <em>(9%+8%)</em></td>
<td>16.2% <em>(6.1%+10.1%)</em></td>
</tr>
<tr>
<td><strong>Overall Survival</strong> <em>(DMTi vs BSC)</em></td>
<td>14 v 14.9 <em>(p=0.636)</em></td>
<td>20 v 11 <em>(p=0.10)</em></td>
</tr>
<tr>
<td><strong>Median Response</strong></td>
<td>10 m</td>
<td>15 m</td>
</tr>
<tr>
<td><strong>Treatment-associated Mortality</strong></td>
<td>14%</td>
<td>≤ 1%</td>
</tr>
</tbody>
</table>

Comparison of Decitabine & Azacitidine Phase 3 Trials

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Decitabine</th>
<th>Azacitidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crossover</td>
<td>NA</td>
<td>53%</td>
</tr>
<tr>
<td>Response Criteria</td>
<td>IWG</td>
<td>CALGB</td>
</tr>
<tr>
<td>% of IPSS Int-2/High</td>
<td>69</td>
<td>NA</td>
</tr>
<tr>
<td>% of prior therapy</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Median duration of MDS (months)</td>
<td>7.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Median number of treatment cycles</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

## Decitabine versus intensive chemotherapy in MDS

<table>
<thead>
<tr>
<th></th>
<th>N° of patients</th>
<th>Response rate</th>
<th>Median survival (Mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive chemotherapy</td>
<td>376</td>
<td>52% CR</td>
<td>11</td>
</tr>
<tr>
<td>Decitabine</td>
<td>115</td>
<td>35% CR (70 % OR)</td>
<td>22</td>
</tr>
</tbody>
</table>

Jabbour, ASH 2006
Azacitidine vs. Decitabine: Practical Considerations

• Azacitidine data shows improvement in overall survival
• Data supports decitabine use after azacitidine failure
• Emetic potential azacitidine > decitabine
• Decitabine as approved needs hospital stay, whereas azacitidine treatment is outpatient

Lenalidomide (Revlimid®)

- Indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk MDS
- Associated with deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities
Lenalidomide MDS-003 Clinical Trial

- **Trial Design**: Multicenter, International
- **Subjects**: 5q31 deletion, low/Int-1 risk, ≥ 2 U PRBC / 8 weeks
- **Arms**: lenalidomide 10mg PO daily vs. lenalidomide 10mg PO daily x 21 d
- **Primary endpoint**: transfusion independence

Lenalidomide in MDS: Results in 5q-

RBC transfusion independence 99/148 (67%) by week 24

Median time to transfusion independence was 4.6 weeks (range 1 - 49)

Median Duration of transfusion independence not reached by median 104 weeks

## Lenalidomide MDS – 003 Adverse Events (N=148)

<table>
<thead>
<tr>
<th>Condition</th>
<th>All Grades (%)</th>
<th>≥ Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>(61.5%)</td>
<td>(50.0%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>(58.8%)</td>
<td>(53.4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>(48.6%)</td>
<td>(3.4%)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>(41.9%)</td>
<td>(2%)</td>
</tr>
<tr>
<td>Rash</td>
<td>(35.8%)</td>
<td>(6.8%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>(31.1%)</td>
<td>(4.7%)</td>
</tr>
</tbody>
</table>

Anti-thymocyte Globulin (ATG) – immunotherapy for MDS

1. May be indicated in low-risk MDS
   HLA-DR15
   (with reduced bone marrow cells)

2. Requires admission to hospital, and hematology team experienced in its use

3. Improves blood counts in 30-50% of cases
Predictive Model for Response to Immunosuppression (ATG ± CSA)

Patient’s Age in Years + Duration of RCTD in Months

<table>
<thead>
<tr>
<th>DR15-negative patients</th>
<th>DR15-positive patients</th>
<th>Predicted Probability of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;57</td>
<td>&gt;71</td>
<td>Low (0-40%)</td>
</tr>
<tr>
<td>≤57</td>
<td>≤71</td>
<td>High (41-100%)</td>
</tr>
</tbody>
</table>

RCTD = red-cell transfusion dependence

BMT for MDS

- Curative-intent therapy for MDS with significant treatment-associated risks.

- Chemotherapy to:
  - Eliminate diseased bone marrow
  - Prevent rejection of the bone marrow transplant
  - 5-7 days (given in hospital)

- Transplant
  - Bone marrow is usually collected on day of transplant
  - Administered through intravenous catheter
BMT COMPLICATIONS

- Regimen-related toxicity
- Infections
- Graft-versus-host disease
  - Donor immune system targets patient
- Relapse
## Life Expectancy: BMT in MDS

<table>
<thead>
<tr>
<th></th>
<th>Transplant at Diagnosis</th>
<th>Transplant in 2 Years</th>
<th>Transplant at Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>6.51</td>
<td>6.86</td>
<td>7.21</td>
</tr>
<tr>
<td>Int-1</td>
<td>4.61</td>
<td>4.74</td>
<td>5.16</td>
</tr>
<tr>
<td>Int-2</td>
<td>4.93</td>
<td>3.21</td>
<td>2.84</td>
</tr>
<tr>
<td>High</td>
<td>3.20</td>
<td>2.75</td>
<td>2.75</td>
</tr>
</tbody>
</table>

Effect of Age on outcome following RIC allogeneic transplant for MDS

Conclusions

1. MDS should be considered in any patient (but particularly the elderly patient) with unexplained cytopenia(s) or monocytosis.

2. Blood smear, bone marrow aspirate, and cytogenetic testing necessary for diagnosis.

3. Treatment is indicated in patients with symptomatic cytopenias.

4. Supportive care is an important adjunct (smoking cessation, immunizations, hygiene, growth factors, transfusions, iron chelation).
Conclusions

5. Patients with low risk disease managed with supportive care ±:
   a) Lenalidomide for 5q- syndrome
   b) Azacitadine / Decitabine
   c) Consider ATG for DR15+, low RBC transfusions

6. Patients with high risk disease managed with supportive care ±:
   a) Azacitadine / Decitabine
   b) Transplant eligible patients should be referred for transplant evaluation.
Questions......