Treating Lower-Risk Myelodysplastic Syndrome (MDS)

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Outline

- Case Study
- What is lower-risk MDS?
- Classification systems
- Prognosis
- Treatment Strategies
- Future Directions

Case Study

- 50 year old man with no significant past medical history presents with worsening fatigue and is found to have anemia.
- GI workup is normal.
- No vitamin deficiencies or other sources of chronic bleeding. No congenital anemia.
- Bone marrow shows dysplasia.
- Cytogenetics or chromosomes show 20q-
What is Lower Risk MDS?

- Patients may have only mild decrease in blood counts, little or no transfusion requirement, evidence of dysplasia.

- Classification Systems: FAB, WHO, IPSS

- International Prognostic Scoring System (IPSS)
  - Low risk
  - Intermediate – 1
  - Intermediate – 2
  - High Risk

### FAB Classification:

<table>
<thead>
<tr>
<th>Name</th>
<th>BM Blasts (%)</th>
<th>PB Blasts (%)</th>
<th>Ringed Sideroblasts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory Anemia (RA)</td>
<td>&lt; 5</td>
<td>≤ 1</td>
<td>&lt; 15</td>
</tr>
<tr>
<td>Refractory Anemia with Ringed Sideroblasts (RARS)</td>
<td>&lt; 5</td>
<td>≤ 1</td>
<td>≥ 15</td>
</tr>
<tr>
<td>Refractory Anemia with Excess Blasts (RAEB)</td>
<td>5 – 20</td>
<td>&lt; 5</td>
<td>Variable</td>
</tr>
<tr>
<td>Refractory Anemia with Excess Blasts in Transformation (RAEB-T)</td>
<td>21 – 30</td>
<td>≥ 5</td>
<td>Variable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FAB Classification</th>
<th>Median Survival (years)</th>
<th>Risk of Evolving to AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>3.6</td>
<td>15 %</td>
</tr>
<tr>
<td>RARS</td>
<td>6.1</td>
<td>5 %</td>
</tr>
<tr>
<td>RAEB</td>
<td>1.0</td>
<td>40 %</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>0.4</td>
<td>60 %</td>
</tr>
<tr>
<td>CMML</td>
<td>1.7</td>
<td>35 %</td>
</tr>
</tbody>
</table>


### World Health Organization MDS Categories (2008)

<table>
<thead>
<tr>
<th>Name</th>
<th>Key Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia</td>
<td>Anemia and erythroid dysplasia</td>
</tr>
<tr>
<td>Refractory anemia with ring sideroblasts</td>
<td>&gt; 15% ring sideroblasts</td>
</tr>
<tr>
<td>Refractory anemia with multilineage dysplasia</td>
<td>Multilineage dysplasia with &gt;1 cytopenia 10%</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 1</td>
<td>5-9% blasts</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 2</td>
<td>10-19% blasts; &gt;Auer rods</td>
</tr>
<tr>
<td>Unclassifiable MDS</td>
<td>Does not fit other categories</td>
</tr>
<tr>
<td>Childhood MDS</td>
<td>Hypoplastic hematopoiesis</td>
</tr>
</tbody>
</table>

FAB and WHO Classifications

<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>Erythropoietic</td>
</tr>
<tr>
<td></td>
<td>RCUD (RA, RN, RT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RCMD</td>
<td>2-3 lineages</td>
</tr>
<tr>
<td></td>
<td>MDS-U</td>
<td>1 lineage</td>
</tr>
<tr>
<td>RARS</td>
<td>RARS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RCMD-RS</td>
<td>Erythropoietic</td>
</tr>
<tr>
<td></td>
<td></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></td>
<td>RAEB-2 (10-19%)</td>
<td>1-3 lineages</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>AML</td>
<td></td>
</tr>
</tbody>
</table>

International Prognostic Scoring System (IPSS):

- Based on outcomes for 816 untreated primary MDS patients from large national trials
- CMML (WBC >12,000/µl) was excluded
- Intent to define patients with similar outcomes based on risk factors despite disparate morphology
- Risk factors used: cytogenetics, FAB, % blasts, cytopenias, age, sex and two previous scoring systems
- Multivariate analysis allowed development of a score


<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM blasts (%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Karyotype</td>
<td>0</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0.5</td>
</tr>
</tbody>
</table>

IPSS for MDS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM blasts (%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Karyotype</td>
<td>0.0</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Cytoopenia: Neutrophils <1,500/µl, Hemoglobin <10 g/dl, Platelets <100,000/µl.

<table>
<thead>
<tr>
<th>Karyotype Category</th>
<th>Chromosomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Normal, Y, del(5q), del(20q)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>All others</td>
</tr>
<tr>
<td>Poor</td>
<td>Complex (≥ 3 abnormalities), chromosome 5 abnormalities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate 1</td>
<td>0.5 - 1.0</td>
</tr>
<tr>
<td>Intermediate 2</td>
<td>1.5 - 2.0</td>
</tr>
<tr>
<td>High</td>
<td>≥ 2.5</td>
</tr>
</tbody>
</table>

Survival of MDS Patients by IPSS

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Int – 1</th>
<th>Int – 2</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (yrs)</td>
<td>5.7</td>
<td>3.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60</td>
<td>11.8</td>
<td>5.2</td>
<td>1.8</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>4.8</td>
<td>2.7</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Risk of 25% Evolving to AML

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Int – 1</th>
<th>Int – 2</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time to Transform (yrs)</td>
<td>9.4</td>
<td>3.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60</td>
<td>&gt; 9.4</td>
<td>6.9</td>
<td>0.7</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>9.4</td>
<td>2.7</td>
<td>1.3</td>
</tr>
</tbody>
</table>

IPSS

The IPSS Risk Classification allows a simple method to stratify patients into 4 groups that segregate for:
- Overall Survival
- Risk of evolution to AML

Most useful clinical tool, but has its drawbacks:
- Primary MDS only
- Not validated for CMML
- Ideally used at time of diagnosis in untreated pts.
- Doesn’t take into account transfusion requirements or severity/weight of cytopenias.

Prognosis in Low Risk MDS

<table>
<thead>
<tr>
<th>Score</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>80</td>
</tr>
<tr>
<td>≥ 3-4</td>
<td>27</td>
</tr>
<tr>
<td>≥ 5</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse cytogenetics</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 60</td>
<td>2</td>
</tr>
<tr>
<td>Hgb &lt; 10</td>
<td>1</td>
</tr>
<tr>
<td>Platelets &lt; 50</td>
<td>2</td>
</tr>
<tr>
<td>Platelets 50-200</td>
<td>1</td>
</tr>
<tr>
<td>BM Blasts ≥ 4%</td>
<td>1</td>
</tr>
</tbody>
</table>

Treatment Options

- Watch and Wait (Observation)
- Supportive Care, Transfusions, Iron Chelation
- Growth Factors
  - Erythropoetin (Procrit, Aranesp)
  - G-CSF (Neupogen, Neulasta)
  - Thrombopoiesis agents?
- Immunosuppressive Therapy
  - ATG, Cyclosporine, Steroids
- Lenalidomide (Revlimid)
- Chemotherapy?

Goals of Treatment

- Control symptoms and morbidities associated with low blood counts
- Improving or maintaining quality of life
- Improving overall survival and decreasing risk of progression to AML.
- In general, MDS is an incurable illness.
Factors in Selecting Treatment

- Age (≤ 60 vs. > 60)
- Performance Status
  - Level of functioning
- Co-morbid conditions
- IPSS-defined risk group

Watch and Wait Approach

- Many patients with Lower Risk MDS can be observed without treatment
- No data yet that earlier treatment improves outcomes in patients with lower risk MDS
- In patients with minimal transfusion dependence and few complications related to low blood counts, observation is an important approach.
- Blood counts every 2-3 months. Bone marrow every 6-12 months or as needed.

Supportive Care

- Packed Red Blood Cell (PRBC) Transfusions
  - Goals:
    - Increase oxygen carrying capacity
    - Improve symptoms, quality of life.
  - General Guidelines:
    - Hemoglobin < 8.6 or for symptomatic anemia.
    - Higher threshold (<10) for patients with significant cardiopulmonary disease.
  - Side effects
    - Transfusion reactions
    - Volume overload
    - Iron overload
    - Small risk of viral transmission
Supportive Care

- **Platelet Transfusions**
  - Goals:
    - Reduce risk of bleeding complications
  - General Guidelines:
    - Vary from platelets <15 or 20 depending on freq. of followup
    - Also transfuse in preparation for procedures or surgery
  - Side effects
    - Transfusion reactions
    - Bacterial infection
    - Platelet alloimmunization (platelet resistance)
- **Antibiotics**
  - Prophylactic/Preemptive vs. As needed

What about Iron Overload?

- 1 unit of PRBCs contains 250 mg of Iron.
  - Normal body requirement for iron is 1-2mg/day.
  - Pregnant or menstruating women - slightly higher at 2-4mg/day
- The body has no good way of getting rid of iron.
- Easiest and most widely used method to measure iron overload is: Ferritin level
  - Drawbacks; other methods.

Iron Overload

- Patients with congenital disorders (eg. transfusion dependent thalassemias, hemachromatosis) develop long standing iron overload.
- Complications from many years of end-organ exposure to iron
  - Liver, Heart, Gonads, Pancreas.
  - Iron chelation therapy proven to benefit in these patients.
- Most MDS patients have a shortened overall life expectancy
  - Does iron chelation benefit these patients?
Iron Overload in MDS

- Level of transfusion dependence is prognostic in MDS
- Higher transfusion requirements correlate with lower overall survival
- Ferritin level has also been correlated with overall survival in MDS.
- Does this necessarily mean that iron overload correlates adverse overall survival?
- Could ferritin be a marker of higher transfusion requirements?
- Ferritin is also a marker of inflammation (acute phase reactant)

Iron chelation therapy improves survival in MDS patients: matched-pair analysis

- Matched pair retrospective analysis.
  - 93 patients who received chelation
  - 93 patients who received supportive care
- Serum ferritin ≥ 500 µg/dL
- Improved overall survival in patients who received chelation versus not (74 months vs. 49 months)
- No difference in risk of transforming to AML.

Iron chelation therapy improves survival in MDS patients: matched-pair analysis

Overall survival

Cumulative survival

No chelation

Chelation

Months

Overall survival

0.0
0.2
0.4
0.6
0.8
1.0
0
18
36
54
72
90
108
126
144
162
180
198
216
234
252
270
288
306
324
342
360

Cumulative risk of AML transformation

No chelation

Chelation

Months

AML transformation

0.0
0.2
0.4
0.6
0.8
1.0
0
18
36
54
72
90
108
126
144
162
180
198
216
234
242
260
278
296
314
332
350
368
386
404
422

Median cumulative survival

Chelation therapy: 75 months
No chelation: 43 months

Cumulative risk of AML transformation

Chelation therapy: 15% at 5 years
No chelation: 18% at 2 years
19% at 5 years

Effect of iron chelation therapy in MDS patients - France

- Patients with low or intermediate-1 risk MDS (IPSS) who required regular transfusions.
- 53 pts received chelation, 44 did not.
- Overall survival 124 months vs. 53 months.
- Effect was more important in heavily transfused pts and younger pts.
- No significant differences in specific causes of death.
- Retrospective study
  - Better prognosis pts received chelation
  - Need prospective randomized trials

Iron chelation therapy improves survival in MDS patients

Iron Chelation

- Molecules that bind tightly to metal ions, making them inert and facilitating excretion.
- Desferoxamine (Desferral)
  - Continuous SQ or IV infusion
  - Diarrhea, dizziness, nausea, severe allergic rxn
- Desferasirox (Exjade)
  - Oral; dissolvable in water or juice
  - GI disturbance, Rash, kidney failure, liver dysfunction

Median overall survival
- 53 months in non-chelated patients
- 124 months in chelated patients

Survival distribution function

Time from diagnosis to death (months)

Non-chelated
Chelated
p < 0.0003

Iron chelation therapy improves survival in MDS patients
Exjade Boxed Warning

**WARNING: RENAL, HEPATIC FAILURE AND/OR GASTROINTESTINAL HEMORRHAGE**

Exjade may cause:
- renal impairment, including failure
- hepatic impairment, including failure
- gastrointestinal hemorrhage

In some reported cases, these reactions were fatal. These reactions were more frequently observed in patients with advanced age, high risk myelodysplastic syndromes (MDS), underlying renal or hepatic impairment or low platelet counts (≥50 x 10^3/μL) [see Contraindications (5.2), Warnings and Precautions (5.2 - 5.7)].

Exjade therapy requires close patient monitoring, including measurement of:

- serum creatinine and/or creatinine clearance prior to initiation of therapy and monthly thereafter; in patients with underlying renal impairment or risk factors for renal impairment, monitor creatinine and/or creatinine clearance weekly for the first month, then monthly thereafter;
- serum transferrin and ferritin prior to initiation of therapy, every two weeks during the first month and monthly thereafter.

Growth Factors

- **Erythropoietin**
  - Stimulates RBC production
  - Procrit
  - Aranesp

- **Granulocyte-Colony Stimulating Factor (G-CSF)**
  - Stimulate WBC production
  - Neupogen
  - Neulasta

Growth Factors

- EPO combined with myeloid cytokines have synergistic effects on erythropoiesis in vitro.

- Several phase II trials have shown clinical synergy of EPO combined with G-CSF

- Randomized Phase III Trials have confirmed increased response and reversal of resistance when EPO and G-CSF are given together

- RR is about 16-40% vs. 50-73% in favor of combination.
Model to predict response to growth factors

- Serum EPO ≤ 500 U/L & transfusion need of < 2 units of PRBCs per month
  - High probability of response
- Serum EPO > 500 U/L & transfusion need of ≥ 2 units of PRBCs per month
  - Poor response to growth factors
- Presence of either conferred an intermediate response.
- ORR = 42% (61% in high response group vs. 14% in low response group)


EPO + GCSF May Improve Survival in MDS with Low RBC Tx Needs

- Comparison of:
  - Nordic studies (EPO+GCSF; n=121)
  - Italian cohort (no EPO; n=237)
- Erythroid response rate = 39%
- Median response duration 23 months
- Better response rate and survival in patients who had a lower transfusion requirement (< 2 units of PRBCs / month)


EPO + GCSF May Improve OS

Low transfusion requirement

High transfusion requirement

Immunosuppressive Therapy

- In some cases of MDS, self directed immunity may play a role in the ineffective hematopoiesis. ("hypoplastic MDS")
- Autoimmune T-cells may be involved in the pathophysiology. (ie. aplastic anemia)
- Immunosuppressive therapy directed at these T-cells may play a role in improving blood counts and reducing transfusion requirements.

Immunosuppression

- ATG reversed transfusion dependence in 34% of patients treated with ATG.
- Several studies have shown response to single agent Cyclosporine A.
  - RR = 37% - 100%

| Table 2. Comparison of response to CSA in various studies |
|-----------------|-----------------|-----------------|
| Jonasova et al. | S. Molldrem et al. | Saunthararajah et al. |
| (7)            | (10)            | (12)          |
| Total subjects | 17              | 16             | 14            |
| RA              | 16              | 4              | 4             |
| Hypoplastic     | 8               | 8              | 4             |
| Variable        | Variable        | Variable       |
| Major response  | 14              | 4              | 4             |
| Time to onset   | 3               | 1.5            | 2.5           |
| (months)        |                 |                |               |
| Side effect     | 3               | Nil            | Nil           |
| (Nil)           |                 |                |               |

Immunosuppression

- Responses to immunosuppression tend to favor low risk MDS, younger age, and those with HLA-DR15.
- A regimen of ATG, Cyclosporine and Prednisone achieved an Overall response rate of 16% with 4 (13%) complete remissions.
**Immune Modulatory Therapy**

- **Lenalidomide (Revlimid)**
  - Immunomodulatory agent related to thalidomide
  - Approved for treatment of Multiple Myeloma and transfusion dependent MDS.

- **Lenalidomide study in transfusion patients with transfusion dependent MDS**
  - 43 pts with most low, int-1 MDS were treated
  - Dose: 10mg vs. 25mg vs 10mg x 21d
  - Response rate = 56% (dec. transfusion dependence)
  - Highest response rate (83%) in patients with 5q-


**Lenalidomide in 5q- MDS**

- Multicenter trial of lenalidomide in patients with MDS associated with a 5q- cytogenetic abnormality
  - 148 patient treated
  - 10 mg daily x 28 day vs. 10 mg daily x 21 days
  - 67% Response Rate (reduced PRBC transfusion dependence)
  - Responses were rapid and durable
  - Cytogenetic response were highest (77%) in patients with isolated 5q- abnormality and decreased with additional chromosome abnormalities

- **Adverse Effects**
  - Neutropenia, thrombocytopenia
  - Risk of thrombosis


**Future Directions**

- Appropriately stratify low risk patients who may need more aggressive therapy.
  - Low Dose chemotherapy?
    - Very low dose decitabine.
  - Directing therapy at reactive oxygen species?
  - Novel molecules targeting signalling pathways inside the malignant cells.
    - MAP kinase, PI3 Kinase.