Treating Higher-Risk Myelodysplastic Syndromes

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Case Report: Patient #1

- 76 year-old man with fatigue, bruising
- Doctor evaluation
  - Blood counts are low
    - Hemoglobin 8 g/dL
    - Platelet count 60,000/ul
    - White cell count 2,000/ul, 45% neutrophils
  - Referral to hematologist/oncologist
- Bone marrow evaluation
  - Hypercellular marrow
  - Severe dysplasia – red cells, white cells, platelets
  - 8% blasts
  - Chromosome analysis → +8
Patient #1 (continued)

• Diagnosis: Myelodysplastic Syndrome
• Concerning features:
  – All the blood cells are affected; red cells, white cells, platelets
  – Blast percentage is increased
  – Chromosomes are abnormal

Assessing Prognosis of MDS

• Concerning features
  – How severely are the blood counts affected?
  – How many blasts are there?
  – What chromosomes are affected?

• Prognostic Scoring Systems
  – IPSS
  – IPSS-R
  – WHO
  – MDACC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow blasts (percent)</td>
<td>&lt;5</td>
<td>3 to 10</td>
<td>-</td>
<td>11 to 20</td>
<td>21 to 50</td>
<td></td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cytopenias*</td>
<td>0/1</td>
<td>2/3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk group</th>
<th>IPSS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5 to 1.0</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5 to 2.0</td>
</tr>
<tr>
<td>High</td>
<td>2.5 to 3.5</td>
</tr>
</tbody>
</table>

*Blood 1997; 89:2079
Our patient's score: 1.5 = Int-2


Our patient's score: 5.5 = high
Treatment Options

- Supportive Care
- Hypomethylating agents
  - Azacytidine (Vidaza)
  - Decitabine (Dacogen)
- Intensive chemotherapy
- Allogeneic stem cell transplantation
- Clinical trials

Supportive Care

- Transfusions of red cells and platelets
- Darbepoetin alfa (Aranesp)
- Watch for infection

Hypomethylating Agents

- Azacitadine (Vidaza)
- Decitabine (Dacogen)
- Mild chemo
  - Believed to work differently from usual chemotherapy
  - Fairly well-tolerated
- Response to treatment (Vidaza, Dacogen is similar)
  - 38% improved
  - 17% partial or complete remission
  - Survival prolonged by 10 months
  - %age of patients alive at 2 years greater (51 vs. 26%)
Azacytidine (Vidaza)

- **Dose:** 75 mg/m² IV or subcutaneously for 7 days every four weeks
  - Alternative schedules
    - 75 mg/m² x 5 days (M-F), rest S/S, x 2 days (M-T)
    - 75 mg/m² x 5 days (M-F)

- **Side effects**
  - Decreased blood counts
  - Nausea

Decitabine (Dacogen)

- **Dose:** 20 mg/m² IV M-F every 28 days
  or 15 mg/m² IV every 8 hours for three days every 6 weeks

- **Side effects**
  - Decreased blood counts
  - Nausea

Hypomethylating Agents

**Important Points**

- Give at least 4 cycles before deciding it is not working
- Can be difficult to sort out the cause of worsening blood counts: is it due to the disease or treatment of the disease?
- If a response, then continue indefinitely
Our Patient

- Receives Azacytidine (Vidaza) for 2 cycles
  - Blood counts are no better
  - What should be done?
- Receives Azacytidine for 2 more cycles
  - Frequency with which he needs red cell and platelet transfusions seems to be decreasing
  - WBC seems to be increasing
  - Decision to continue treating

Continued

- Receives 2 more cycles
  - Now is clearly improved – receiving no transfusions, WBC clearly better
  - Should we stop or continue?
- What if he has 6 cycles and is just clearly not responding?
- Two weeks after the second cycle of treatment, he had a fever of 102 with chills at 1 a.m.
  - What should he do?

Case Report: Patient #2

- 60 year-old man
- Decreased exercise tolerance
- CBC → low blood counts
- Bone marrow → MDS, 10% blasts, concerning cytogenetics
- Prognostic score → high risk disease
- Treatment?
Allogeneic Stem Cell Transplantation

- Pro: Potential cure of disease
- Con: Very difficult process, risk of infection, organ damage, graft vs. host disease

Allogeneic Stem Cell Transplantation for MDS

Outcomes

- Figure S5: Impact of IPSS score on disease-free survival for transplanted MDS patients.
Allogeneic Stem Cell Transplantation for MDS
Outcomes

TIMING OF TRANSPLANT?

Blood. 2004;104:579-585

Figure 5A: Impact of IPSS score on non-relapse mortality for transplanted MDS patients.
Patient #2: Continued

• Patient given supportive care
• Search for donor
  – No suitable family match
  – Unrelated donor registry – promising
• In the meantime, patient developed acute leukemia
• Given intensive chemotherapy to control disease, got into remission
• Stem cell transplantation
  – High dose chemotherapy
  – Allogeneic stem cells from unrelated donor
  – Outcomes: prompt engraftment, mild controllable GVHD, mild infections, disease in remission 1 year later

Case Report: Patient #3

• 68 year-old woman diagnosed with high risk MDS. Has a matched sibling donor
• Can she have a transplant?

Reduced-Intensity Transplants (aka nonmyeloablative, mini)
Reduced-Intensity Transplants for MDS

- Patient #3 – 68 year-old female: great outcome
- Patient #4 – 68 year-old female: severe GVHD and death

Blood. 2009;104:1616-1623

Allogeneic SCT for MDS: Weighing in the Balance

- No SCT
- SCT

1. High risk disease
   - Younger
   - Healthier
   - Better match
2. Lower risk for SCT
3. Lower risk disease
   - Older
   - Sicker
   - Worse match

What About Intensive Chemotherapy?

- Is considered for younger, healthier patients with high percentages of blasts (e.g. >10%)
- Perhaps 50% get a remission. Is toxic, with 15% dying during treatment
- Perhaps useful as a bridge to getting a transplant, but uncertain benefit if transplant is not in the picture
- We reserve for highly selected patients
Summary: Treatment Options For Higher-Risk MDS Patients

- **Supportive care alone** (transfusions, antibiotics, Aranesp)
  - Pros: gentler
  - Cons: doesn’t alter disease course

- **Hypomethylating agents**
  - Pros: good response in some patients, fairly well tolerated
  - Cons: most patients don’t respond that well

- **Allogeneic SCT**
  - Pros: potential for cure
  - Cons: very toxic, risk of death

- **Intensive chemotherapy**
  - Pros: can partially control disease
  - Cons: very toxic, risk of death, no curative potential

Different Choices for Different Higher-Risk Patients

- **81 year-old man. Congestive heart failure.**
  - Supportive care

- **72 year-old woman. Otherwise fairly healthy.**
  - Supportive care + hypomethylating agents

- **55 year-old man. Otherwise healthy.**
  - Allogeneic SCT with full-dose regimen (maybe intensive chemotherapy first if he has a fairly high percentage of blasts)
  - Allogeneic SCT

- **60 year-old woman. Very sick with numerous other medical conditions.**
  - Supportive care – alone or perhaps with hypomethylating agents

- **66 year-old man. Otherwise healthy.**
  - Reduced-intensity SCT

Patient #5

- **60 year-old woman**
- **High risk MDS**
- **High risk SCT**
- **Patient chooses not to have SCT**
- **Analysis of bone marrow**
  - MDS
  - Blasts driven by FLT3
- **Treatment**
  - Azacitidine
  - FLT3 inhibitor – 1st generation
- **Response**
  - Partial improvement in blood counts
  - Blasts go away
- **Research ongoing that might help our patient**
  - Better FLT3 inhibitors
  - Better transplant techniques
- **Other experimental approaches**
  - New insights
  - New treatments