TREATMENT OF HIGH RISK MDS AND THE INDICATION FOR STEM CELL TRANSPLANT

Prapti Patel, MD
Assistant Professor of Internal Medicine
Division of Hematology Oncology
University of Texas Southwestern
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Outline

- Definition of high risk MDS
- Hypomethylating agents
- Stem cell transplant
- Pre-transplant hypomethylating agents
- Post-transplant hypomethylating agents
- Clinical trials available at UTSW
What is High Risk MDS?

- Defined by R-IPSS
  - blast count
  - Number of cytopenias
  - Cytogenetic abnormalities

- What does it mean for the patient:
  - High risk of complications
  - High risk of transformation to acute leukemia
Refractory Anemia with Excess Blasts - 2.

Pelger Huet Anomoly

Blast

Peter Maslak, ASH Image Bank 2011; 2011-2536
% BM Blasts and Risk of Transformation to AML
Cytogenetics Abnormalities in MDS

A

Cytogenetic Subtypes

Survival

No. of
patients (%)

-Y
17 (2)
del(5q)
48 (6)
Normal
489 (60)
del(20q)
16 (2)
Misc single
74 (9)
x8
38 (5)
Double
20 (2)
Misc double
14 (2)
Chrom J abn
10 (1)
Misc complex
15 (2)
Complex
66 (8)

B

AML Evolution
### Table 3. IPSS-R prognostic score values

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Cytogenetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Very poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>BM blast, %</td>
<td>≤ 2</td>
<td></td>
<td>&gt; 2%&lt; 5%</td>
<td></td>
<td>5%-10%</td>
<td>&gt; 10%</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥ 10</td>
<td></td>
<td>8&lt; 10</td>
<td></td>
<td>&lt; 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 100</td>
<td>50&lt; 100</td>
<td></td>
<td>&lt; 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>≥ 0.8</td>
<td></td>
<td>&lt; 0.8</td>
<td></td>
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</tbody>
</table>

### Table 4. IPSS-R prognostic risk categories/scores

- **Very good**: -Y, del(11q)
- **Good**: Normal, del 20q, del 5q, del 12p
- **Intermediate**: +8, 7q-, 1(17q), +19, +21
- **Poor**: -7, del3(3)q21/q26, complex (3 abnormalities)
- **Very poor**: >3 abnormalities
### IPSS-R

#### Table 5. IPSS-R prognostic risk category clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Very low</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Very high</th>
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</thead>
<tbody>
<tr>
<td>Patients, %</td>
<td>7012</td>
<td>19</td>
<td>38</td>
<td>20</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Survival, all*</td>
<td></td>
<td>8.8</td>
<td>5.3</td>
<td>3.0</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7.8-9.9)</td>
<td>(5.1-5.7)</td>
<td>(2.7-3.3)</td>
<td>(1.5-1.7)</td>
<td>(0.7-0.8)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.5</td>
<td>1.0</td>
<td>2.0</td>
<td></td>
<td>3.2</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.46-0.59)</td>
<td>(0.93-1.1)</td>
<td>(1.8-2.1)</td>
<td>(2.9-3.5)</td>
<td>(7.2-8.8)</td>
</tr>
<tr>
<td>Patients, %</td>
<td>6485</td>
<td>19</td>
<td>37</td>
<td>20</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>AML/25%*†</td>
<td>NR</td>
<td>10.8</td>
<td>3.2</td>
<td></td>
<td>1.4</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(14.5-NR)</td>
<td>(9.2-NR)</td>
<td>(2.8-4.4)</td>
<td>(1.1-1.7)</td>
<td>(0.7-0.9)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.5</td>
<td>1.0</td>
<td>3.0</td>
<td></td>
<td>6.2</td>
<td>12.7</td>
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<tr>
<td></td>
<td></td>
<td>(0.4-0.6)</td>
<td>(0.9-1.2)</td>
<td>(2.7-3.5)</td>
<td>(5.4-7.2)</td>
<td>(10.6-15.2)</td>
</tr>
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Therapy of MDS

Low Risk

- Goal: try to increase the function of the normal cells in the bone marrow
- Method: myeloid growth factors

High Risk

- Goal: killing neoplastic clone causing MDS and preventing transformation to AML
- Method:
  - Hypomethylating agents
  - Allogeneic stem cell transplant
High Risk MDS Treatment: Azacitdine

- Randomized phase III study of SQ Aza in all stages of MDS
  - BSC v Aza 75 mg/m2 D1-7 Q 28 days x 4 cycles

<table>
<thead>
<tr>
<th></th>
<th>BSC</th>
<th>AZA</th>
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<tr>
<td># pts</td>
<td>92</td>
<td>99</td>
</tr>
<tr>
<td>CR</td>
<td>0 (0%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>PR</td>
<td>0 (0%)</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>Improved</td>
<td>5 (5%)</td>
<td>37 (37%)</td>
</tr>
<tr>
<td>Total</td>
<td>5 (5%)</td>
<td>60 (60%)</td>
</tr>
<tr>
<td>Time to AML</td>
<td>12 months</td>
<td>21 months</td>
</tr>
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</table>

- When using the IWG IPSS criteria, the response rate fell to 40-50%

• Better treatments needed!
Azactadine Survival Study

- Randomized Phase III
  - AZA 75 mg/m² z 7 days Q28D (n=179)
  - Conventional Care (BSC, low dose AraC of 20 mg/m²/d x 14d q 28-42 days, standard induction chemo)

- 2 y OS
  - 51 v 26%

What if we could provide a curative option early?

Purpose of Allo Transplant

- Clean, chemo-naïve stem cells
- Graft versus tumor effect
- More effective in treating aggressive malignancies that may not be cured by chemotherapy alone
Only 1 stem cell needed to repopulate entire bone marrow

Only 1 in 1 million leukemic blasts is stem cell, can result in sustained leukemia

stem cells:
- Low proliferative potential
- Chemoresistant
Graft vs Tumor Effect

- Allogeneic grafts initiate immune reactions against host tissue based on the proteins that are on WBC (known as human leukocyte antigens, HLA)
- Severity of reaction depends on degree of incompatibility of the HLAs
- Mediated by T Cells
  - Recipient T cells can recognize donor T cells as foreign and reject graft
  - Donor T cells recognize recipient antigens as foreign/aberrant and cause GVHD/GVT
HLA typing
The Allogeneic Transplant Process

1. **Collection**
   Stem cells are collected from the patient's bone marrow or blood.

2. **Processing**
   Bone marrow or peripheral blood is taken to the processing laboratory where the stem cells are concentrated and prepared for the freezing process.

3. **Cryopreservation**
   Bone marrow or blood is preserved by freezing (cryopreservation) to keep stem cells alive until they are infused into the patient's bloodstream.

4. **Chemotherapy**
   High dose chemotherapy and/or radiation therapy is given to the patient.

5. **Infusion**
   Thawed stem cells are infused into the patient.

**Donor**

**Patient**
Peripheral Blood Collection

**Apheresis: Harvesting Stem Cells From Peripheral Blood**

- Whole blood is collected from donor.
- Blood, minus stem cells, is returned to donor.
- Blood-forming stem cells.
When to transplant?

- Recommendations by ASBMT consensus statement
  - Early transplant:
    - High risk patients
    - Low risk patients that are refractory to treatment
  - No recs on:
    - Induction chemo
    - Type of donor
    - Preparative regimen
### Timing of Transplant and Survival (yrs)

<table>
<thead>
<tr>
<th></th>
<th>Immediate SCT</th>
<th>SCT in 2 yrs</th>
<th>SCT at PD</th>
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<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>

- **Downsides to this analysis:**
  - Done before the age of HMAs (would treatment with an HMA change survival?)
  - Only included patients <60
  - Only included patients that received high dose chemotherapy, therefore more transplant related mortality

Treatment Options for Patients Who are Unfit for Allogeneic Stem Transplant

- Many are not candidates for allogeneic stem cell transplant
- Can’t tolerate complications of transplant: infection, GVHD, chemotherapy toxicity
  - Other medical problems
  - Age (>72 years)
- No treatment that is curative other than stem cell transplant.
  - New treatments on the horizon in the form of clinical trials

There is hope!!
Clinical Trials at UT Southwestern

- First Line treatments
  - Combination therapy with HMA and new medications
- Relapsed refractory treatments
  - Immunotherapies
  - Targeted therapies
- PRECISION MEDICINE in MDS
  - STOP MDS Trial
- Oral HMA!!
Summary

- High risk MDS is defined by low counts, high blasts, and lots of chromosome abnormalities.
- Must be treated because there is a high risk of transformation to acute leukemia and complications from low counts.
- Hematopoietic stem cell transplant is the only curative option.
  - Timing is important
  - Can give post transplant HMA to help prevent relapse.
- Lots of new therapeutic options are available.