Navigating Higher-Risk Myelodysplastic Syndromes

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MDS Goals of Treatment

- Improve blood counts
- Decrease symptoms
- Improve quality of life

- Change natural history
- Prevent progression to AML
- Improve overall survival
Management of Higher-risk MDS

Risk Model

Higher-risk disease

Transplant candidate

No

HMA +/- new drug

Clinical trial

Yes

Donor available

+/- HMA or chemotherapy

Transplant
Gene hypermethylation in MDS

Expressed (or ready for expression)

Silenced

Adapted from Issa, JP
Hypomethylating cytosine analogs

Cytosine

5-methyl-cytosine

Azacytidine

Decitabine

First randomized study of azacitidine in patients with MDS

75 mg/m²/d SC x 7 days every 4 weeks

Responses (after 4 cycles)

Complete remission - 7%
Partial remission - 16%
Improved - 37%
Total - 60%

Survival Probability

Azacitidine
Supportive Care

Log rank P=0.03

Azacitidine survival study in higher-risk MDS

Screening/Central Pathology Review

Investigator CCR Treatment Selection

Randomization

AZA 75 mg/m²/d x 7 d q28 d

CCR (Conventional Care Regimen)

- Best supportive care only
- Low-dose Ara-C
- Standard chemotherapy (7 + 3)

Overall Survival in higher-risk: Azacitidine vs CCR

Azacitidine survival benefit by disease categories

<table>
<thead>
<tr>
<th>ITT Subgroups</th>
<th>Total - Event / N</th>
<th>Favors Azacitidine</th>
<th>Favors CCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAEB &amp; RAEB-T: AGE ≥ 65</td>
<td>138 / 240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGÉ: &lt; 65</td>
<td>45 / 100</td>
<td></td>
<td></td>
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<tr>
<td>≥ 65</td>
<td>150 / 258</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 75</td>
<td>50 / 87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>134 / 251</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>61 / 107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAB: RAEB</td>
<td>95 / 207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAEB-T</td>
<td>80 / 123</td>
<td></td>
<td></td>
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<tr>
<td>WHO: RAEB-1</td>
<td>15 / 31</td>
<td></td>
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</tr>
<tr>
<td>RAEB-2</td>
<td>102 / 193</td>
<td></td>
<td></td>
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<tr>
<td>IPSS: INT-2</td>
<td>71 / 146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>98 / 167</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetics: Good</td>
<td>80 / 167</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>38 / 76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>67 / 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karyotype: -7/del (7q)</td>
<td>42 / 57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias: 0/1</td>
<td>20 / 53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/3</td>
<td>167 / 290</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM Blasts: ≥ 5% to &lt; 11%</td>
<td>34 / 61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 11% to &lt; 21%</td>
<td>98 / 192</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 21% to &lt; 31%</td>
<td>58 / 99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH: ≤ 240 U/l</td>
<td>97 / 208</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 240 U/l</td>
<td>94 / 145</td>
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</table>
Azacitidine treatment

- Subcutaneous or intravenous injections daily for 7 [or 5(+2)] days every 28 days
- Median cycles to first response: 2-3
- Response may require 4-6 cycles
- Do NOT need a complete response for benefit
- Responders need to continue treatment to sustain response.
Decitabine- ADOPT study

- Decitabine 20 mg/m2 IV daily for 5 days; 28-day cycles
- Overall response rate 32% (17% complete remission and 15% marrow complete remission)
- Overall improvement rate 51%, including 18% improvement in blood counts.
- Similar response rates in all risk categories.
- 82% of patients who improved showed responses by the end of cycle two.
- Survival advantage not yet demonstrated for decitabine, likely due to inferior study designs.

Testing new treatments

• Test with azacitidine or decitabine to try to increase response rates and duration.

• Test in patients who do not respond to azacitidine or decitabine, or lose response to azacitidine or decitabine
Management of Higher-risk MDS

Risk Model

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New treatments for myelodysplastic syndromes

- Enhance programmed cell death
  -- Venetoclax
- New hypomethylating agent
  -- Guadecitabine (SGI-110)
- Inhibit cell signaling
  -- Rigosertib
- Inhibit mutation signaling
  -- IDH1, IDH2
  -- Spliceosome
- Immunotherapy
  -- Atezolizumab
  -- BITE antibody
Venetoclax

- Recently FDA-approved for use with azacitidine or decitabine in newly diagnosed AML patients who are older and/or unfit for chemotherapy, with significantly higher response rate.
- Clinical trial with azacitidine in higher-risk MDS – data analysis in progress.
Guadecitabine (SGI-110)

- Dinucleotide of decitabine and guanosine
- Longer half life
- Longer exposure
- Protection from degradation
Guadecitabine – Higher-risk and previously treated

<table>
<thead>
<tr>
<th>Response</th>
<th>Prev Treated (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Marrow CR</td>
<td>15/34 (44%)</td>
</tr>
<tr>
<td>HI</td>
<td>11 (20.8%)</td>
</tr>
</tbody>
</table>

Garcia-Manero G, EHA 2016, Abstract P249
Guadecitabine and Atezolizumab following azacitidine/decitabine failure

Figure 1. Guadecitabine + Atezolizumab: Cycles on Treatment

O’Connell et al. ASH 2018
Ivosidenib (AG-120) Induced Durable Remissions and Transfusion Independence in Patients with IDH1-Mutant Relapsed or Refractory Myelodysplastic Syndrome: Results from a Phase 1 Dose Escalation and Expansion Study – DiNardo et al. ASH 2018
Allogeneic hematopoietic stem cell transplantation

• Only treatment currently known to be curative, but cure rate is <50%

• Has been applicable to only a minority of MDS patients because of age, other medical problems and donor availability, but non-myeloablative approach and alternative donors are increasing its applicability.
Allogeneic hematopoietic stem cell transplantation

- **Procedure**
  - High-dose chemotherapy/radiation therapy
  - Transfusion of donor blood/marrow stem cells
- **Donor**
  - Related - HLA-identical; haploidentical
  - Unrelated
- **Sources**
  - Bone marrow
  - Peripheral blood
- **Conditioning**
  - Myeloablative
  - Non-myeloablative
- **Immunologic effects**
  - Graft vs. leukemia
  - Graft vs. host

**Bone marrow harvest**

**Leukapheresis**
Allogeneic hematopoietic stem cell transplantation outcomes

- Acute complications
- Chronic complications
- Relapse
- Cure
Survival by IPSS risk in patients who did or did not undergo transplantation

Transplant decision

- Disease
  - Risk status
  - Chromosomes
  - Mutations
- Donor
  - Matched sibling
  - Matched unrelated donor
  - Half-matched related donor
- Patient
  - Age
  - Medical problems
  - “Performance status”
  - Support system
  - Personal choice
Myelodysplastic syndromes

• Treatable, and treatments change the course of disease.
• Treatment approach depends on presentation.
• Transplant can cure, but indication depends on presentation and on patient-specific factors.
• FDA-approved treatments, all approved in the last 15 years based on recent clinical trials
• Promising new drugs based on new biological insights
• Ongoing importance of clinical trials!!!