Treatment Options for Lower-Risk MDS
Anemia Management Algorithm 2016: Low- or Intermediate 1–Risk MDS

- Assess potential causes of anemia
- RBC transfusion support for symptomatic patients

<table>
<thead>
<tr>
<th>EPO ≤ 500 mU/mL</th>
<th>EPO &gt; 500 mU/mL; RCMD; ≥ 2 U RBC/mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 U RBC/mo</td>
<td>≤ 60 yrs of age, hypocallear marrow, HLA-DR15+, PNH+</td>
</tr>
</tbody>
</table>

- ESA ± G-CSF
- No response or failure of therapy
- IST

- Yes
- No

- AZA, DAC
- Lenalidomide
- Clinical trial

- del(5q)
- Lenalidomide
- AZA, DAC
- Clinical trial

Erythropoietin in MDS

- Response rates to erythropoietin much lower in MDS than in other malignancies
  - Mean response rate: 16% to 20%
  - Predictors for good response were serum EPO level < 500 U/L, nonrefractory anemia with ring sideroblasts subtype, and lack of previous need for transfusion
- Response rates may improve when given in combination with G-CSF (> 40%)

Myelodysplastic Syndromes

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

RA, RARS, RAEB

Score > +1

Good (74%; n = 34)

Score -1 to +1

Intermediate (23%; n = 31)

Score < -1

Poor (7%; n = 29)

Response Probability

Treatment Response Criteria

CR  Stable Hb > 11.5 g/dL

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

Treatment Response Score

<table>
<thead>
<tr>
<th>S-EPO</th>
<th>U/L</th>
<th>Transf</th>
<th>U RBC/mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>100-500</td>
<td>&gt; 500</td>
<td>&lt; 2 units/mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥ 2 units/mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

Lenalidomide

- Thalidomide analogue with immunomodulatory, antiangiogenic, and antineoplastic properties
- Approved for use
  - Transfusion-dependent anemia due to low- or intermediate 1–risk MDS associated with del(5q), with or without additional abnormalities
  - Multiple myeloma in combination with dexamethasone in patients who have received at least 1 previous therapy
**MDS-003: Lenalidomide in MDS With 5q Deletion**

**Eligibility**
- IPSS diagnosed low/int 1 MDS
- del(5q31)
- ≥ 2 U RBC/8 wks
- Platelets > 50,000/µL
- ANC > 500/µL

**Response**
- Yes → Continue
- No → Off study

**Protocol**
- Wk 0: Register
- Wk 4: Lenalidomide 10 mg/day PO
- Wk 24: Response
  - Continue
  - Off study

- Primary endpoint: transfusion independence
- Secondary endpoints: duration of TI, cytogenetic response, minor erythroid response, pathologic response, safety

MDS-003: Response to Lenalidomide Therapy

Erythroid Response
- TI: 99/148 (67%)
- TI + Minor: 112/148 (76%)

Cytogenetic Response
- CCR: 38/85 (45%)
- CCR + PR: 62/85 (73%)


- Median Hgb increase: 5.4 g/dL
- Time to response: 4.6 wks
- Duration of response: > 2 yrs
MDS-002: Phase II Study of Lenalidomide in RBC-Dependent Non-del(5q) MDS

Eligibility

- IPSS diagnosed low/int-1 MDS w/o del(5q) abnormality
- ≥ 2 U RBC/8 wks
- Platelets > 50,000/µL
- ANC > 500/µL

Yes → Continue

No → Off study

Primary endpoint: TI, Hb response

Secondary endpoints: cytogenetic response, safety

Lenalidomide 10 mg/day PO

Lenalidomide 10 mg PO x 21 days

Dose reduction
5 mg QD
5 mg QOD

MDS-002: Response to Lenalidomide Therapy

Erythroid Response

- TI: 56/214 (26%)
- TI + Minor: 93/214 (43%)

Cytogenetic Response

- CCR: 4/47 (9%)
- CCR + PR: 9/47 (19%)

- Median Hgb increase: 3.2 g/dL
- Time to response: 4.8 wks
- Median duration of response: 41 wks

# MDS-002/003: Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Grade ≥ 3 Adverse Events, %</th>
<th>Non-del(5q)</th>
<th>del(5q)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25</td>
<td>55</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Azacitidine Treatment for Low- or Intermediate 1–Risk MDS

- Pyrimidine nucleoside analogue of cytidine
- Approved for use in MDS of the following subtypes
  - Refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions)
  - Refractory anemia with excess blasts
  - Refractory anemia with excess blasts in transformation
  - Chromic myelomonocytic leukemia
- Causes hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow

Myelodysplastic Syndromes

Randomized Phase II Study of Alternative Azacitidine Dose Schedules

Study Design (N = 151)

Eligibility
- All FAB
- Cytopenia
- ECOG PS: 0-3

5-2-2: 75 mg/m²
(n = 50)

5-2-5: 50 mg/m²
(n = 51)

5: 75 mg/m²
(n = 50)

x 6

12 Cycles
AZA x 5 days q4-6 wks

IWG 2000 HI

## Alternate Azacitidine Dose Schedule Study: Frequency of Major HI

<table>
<thead>
<tr>
<th>Parameters in Evaluable Pts,* n/N (%)</th>
<th>5-2-2 (n = 50)</th>
<th>5-2-5 (n = 51)</th>
<th>5d (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid&lt;sub&gt;Ma&lt;/sub&gt;</td>
<td>19/43 (44)</td>
<td>19/43 (44)</td>
<td>20/44 (46)</td>
</tr>
<tr>
<td><strong>RBC-TI</strong></td>
<td><strong>12/24 (50)</strong></td>
<td><strong>12/22 (55)</strong></td>
<td><strong>15/25 (64)</strong></td>
</tr>
<tr>
<td>Platelet&lt;sub&gt;Ma&lt;/sub&gt;</td>
<td>12/28 (43)</td>
<td>8/30 (27)</td>
<td>11/22 (50)</td>
</tr>
<tr>
<td>Any HI</td>
<td>22/50 (44)</td>
<td>23/51 (45)</td>
<td>28/50 (56)</td>
</tr>
<tr>
<td>Neutrophil&lt;sub&gt;Ma&lt;/sub&gt;</td>
<td>4/23 (17)</td>
<td>4/23 (17)</td>
<td>9/24 (38)</td>
</tr>
<tr>
<td><strong>Heme AEs &gt; grade 3</strong></td>
<td><strong>33/50 (66)</strong></td>
<td><strong>24/48 (50)</strong></td>
<td><strong>17/50 (34)</strong></td>
</tr>
<tr>
<td>AE Tx delay</td>
<td>34/50 (68)</td>
<td>30/48 (63)</td>
<td>17/50 (34)</td>
</tr>
</tbody>
</table>

*IWG 2000 criteria.

Treatment Options for High-Risk MDS
Treatment Algorithm 2016: Intermediate 2–Risk/High-Risk MDS

Start azanucleosides

- Allogeneic donor
  - Favorable
    - Comorbidities
    - Functional status
    - SCT
  - Unfavorable
    - Continue azanucleosides
    - High-intensity chemotherapy
    - Investigational

- No donor

Adapted from NCCN. Clinical practice guidelines in oncology. MDS. V.1.2016.
Myelodysplastic Syndromes

AZA-001: Trial Design

Physician choice of 1 of 3 CCRs

1. BSC only
2. LDAC (20 mg/m^2/day SC x 14 day q28-42 days)
3. 7 + 3 chemotherapy (induction + 1-2 consolidation cycles)

Stratified by
- FAB: RAEB, RAEB-T
- IPSS: Int-2, high

Azacitidine + BSC
(75 mg/m^2/day x 7 days SC q28 days) (n = 179)

Treatment continued until unacceptable toxicity or AML transformation or disease progression

**AZA-001 Trial: Azacitidine Significantly Improves OS**

- **HR:** 0.58 (95% CI: 0.43-0.77; log-rank $P = .0001$)

Graph showing survival over time for two groups:
- **Azacitidine:** 24.5 mos
- **CCR:** 15.0 mos

Reference:
### AZA-001: Grade 3/4 Adverse Events (≥ 2% of Patients)*

<table>
<thead>
<tr>
<th>Adverse Events, n (%)</th>
<th>Azacitidine (n = 175)</th>
<th>BSC Only (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>159 (91)</td>
<td>70 (69)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>149 (85)</td>
<td>72 (71)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>26 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>100 (57)</td>
<td>67 (66)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>22 (13)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>4 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (1)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*When any grade of the reactions occurs in ≥ 5% of azacitidine-treated patients.

Decitabine for MDS

- Approved for the treatment of patients with MDS:
  - Previously treated or untreated
  - De novo or secondary MDS
  - FAB subtypes (RA, RARS, RAEB, RAEB-T, and CMMoL)
  - Intermediate-1, intermediate-2, and high-risk IPSS groups

- Decitabine 15 mg/m2 IV Q 8 hours Days 1, 2, 3 every 6 weeks

- Decitabine 20 mg/m2 IV QD Days 1-5 every 4 weeks

Decitabine for MDS

Decitabine for MDS

- Phase III trial
- No PFS benefit for all comers
- But improved PFS in
  - INT-2 & High IPSS Risk
  - De novo disease

Decitabine for MDS

- Most common side effects
  - Neutropenia 90%
  - Thrombocytopenia 89%
  - Anemia 82%
  - Fever 53%
  - Nausea 42%
  - Cough 40%
  - Petechiae 53%
  - ...

Salvage Therapy After Azacitidine Failure: GFM and AZA001 Studies

<table>
<thead>
<tr>
<th>Type of Salvage</th>
<th>N</th>
<th>ORR</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>165</td>
<td>NA</td>
<td>3.6</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>122</td>
<td>NA</td>
<td>4.1</td>
</tr>
<tr>
<td>Low-dose chemotherapy</td>
<td>32</td>
<td>0/18</td>
<td>7.3</td>
</tr>
<tr>
<td>Intensive chemotherapy</td>
<td>35</td>
<td>3/22</td>
<td>8.9*</td>
</tr>
<tr>
<td>Investigational therapy</td>
<td>44</td>
<td>4/36</td>
<td>13.2*†</td>
</tr>
<tr>
<td>Allogeneic transplantation</td>
<td>37</td>
<td>13/19</td>
<td>19.5*†</td>
</tr>
</tbody>
</table>

*Log-rank comparison of BSC vs intensive CT ($P = .04$), investigational therapy ($P < .001$), or alloSCT ($P < .001$).
†Comparison of intensive CT vs investigational therapy ($P = .05$), intensive CT vs ASCT ($P = .008$), or IT vs ASCT ($P = .09$).

Questions?