Myelodysplastic Syndromes: What’s on the Horizon?

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Treatment Algorithm

SCT Candidate
Yes
Int-2/High
Low/Int-1
No
Int-2/High

5q-
AlloSCT
LENALIDOMIDE
ATG
DNMTI (e.g., AZA)

No Response
Clinical Trial

What Therapies Have U.S. Patients with MDS Received?

- MDS Foundation Patient Survey (n=359; January-October 2006)
- BMF Consortium National MD Survey (n=154; June 2005-January 2007)
- AAAMDS Int’l Foundation Patient Survey (n=358; March 2009)

Sekeres MA et al. JNCI 2008; 100:1542-1551
Sekeres MA et al. submitted
Epigenetic

- Heritable changes that impact transcription of genes
- Not genetic: i.e., not due to deletions or mutations
- Therefore potentially reversible
- Examples:
  - DNA methylation
  - Post-translational histone modifications

Herman and Baylin NEJM 2003, 349:2042-2054

Promoter methylation in cancer

DNA Methyltransferase Inhibitor (DNMTi) Induced DNA Methylation Reversal

A: T
C: G
G: C

DNA Methyltransferase Inhibitor (DNMTi) Induced DNA Methylation Reversal

Adapted from Silverman L. The Oncologist. 2001;6(S5):8-14.
Open Chromatin/
Transcriptionally
Active

Condensed Chromatin/
Transcriptionally Inactive

Acetylated
Histone tails

Deacetylated
Histone tails

Methylated
CpG Islands

DNA

Methyltransferase

MeCP2/Sin3/HDAC

Azacytosine
nucleoside
ingorporation

Study Design

• Phase I trial of Entinostat/5AC combination
  • Dose finding of both drugs
  • Entinostat PO on days 3, 10
  • "flexible response surface design"

• Correlative studies:
  • Changes in promoter methylation/gene
    expression
  • Expression Profiling
  • H2Ax induction

CR plus PR: Flexible
Response Surface
Responders
- Median time to first response 2 (1 – 5)
  - Median to Best response 4 (2 – 9)
  - Median numbers of cycles administered to responding patients: 18.5 (6 – 51)

- Response by diagnosis
  - MDS: 7/13
  - CMMoL: 1/4
  - AML-TLD: 3/7
  - AML-refractory: 1/4
  - AML-primary refractory: 0/3
  - Total MDS responses: 10/20
  - CR/PR/Trilineage: 5 MDS, 3 AML-TLD

E1905 Intergroup Randomized Phase II
- Randomize
  - Cycle 1
    - 5-azacitidine
    - DNA Damage
      - Methylation (gene-specific)
      - H2AXy
      - ROS
  - Cycle 6
    - Clinical Response
      - CR + PR + HI-TL >30%

E1905: What to expect
ASH 2010 (December)
- How does 10 day aza schedule compare to standard seven day?
- Does addition of entinostat improve outcome?
Classes of HDAC Inhibitors

<table>
<thead>
<tr>
<th>Short-chain fatty acids (SCFA)</th>
<th>Butyrate, phenylbutyrate, Valproic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxamic acids</td>
<td>Trichostatin A, vorinostat, panobinostat, belinostat</td>
</tr>
<tr>
<td>Epoxyketone-containing cyclic tetrapeptides</td>
<td>Trapoxins</td>
</tr>
<tr>
<td>Non-epoxyketone-containing cyclic tetrapeptides</td>
<td>Romidepsin</td>
</tr>
<tr>
<td>Benzamides</td>
<td>entinostat</td>
</tr>
</tbody>
</table>

Current State of HDAC inhibitors

- FDA approved:
  - Vorinostat (hydroxamic acid, pan-HDACi)
  - Romidepsin (depsipeptide, Class I enriched)
  - Valproic acid (small chain fatty acid, Class I)
- Vorinostat and Romidepsin approved for cutaneous T cell lymphoma
- Active in other lymphomas

DNMT/HDAC inhibitor combinations: Myeloid Malignancies (Phase I)

- 5-AC/Sodium Phenylbutyrate- sequential
- DAC/Valproic acid - sequential and concomitant
- 5-AC/entinostat- sequential/overlapping
- 5-AC/MGCD-0103
- 5-AC/VPA (+ATRA)
- 5-AC/Belinostat
- 5-AC/Vorinostat
### Azacitidine Combination Studies

<table>
<thead>
<tr>
<th>Combination</th>
<th>Patient Population</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine + lenalidomide</td>
<td>High-risk MDS (n = 18)</td>
<td>Overall RR: 67% CR: 44%</td>
</tr>
<tr>
<td>Azacitidine + etanercept</td>
<td>MDS (low to high risk) (n = 18)</td>
<td>CR: 72% (13/18)</td>
</tr>
<tr>
<td>Azacitidine + vorinostat</td>
<td>MDS, elderly AML (n = 18)</td>
<td>CR: 50% (9/18)</td>
</tr>
<tr>
<td>Azacitidine + MGCD0103</td>
<td>MDS, R/R AML (n = 52)</td>
<td>CR/CRi: 35%; PR: n = 1 (18/52)</td>
</tr>
<tr>
<td>Azacitidine + romiplostim</td>
<td>Low/int-1 MDS azacitidine or decitabine</td>
<td>Platelet response</td>
</tr>
<tr>
<td>Azacitidine + gemtuzumab</td>
<td>AML/high-risk MDS (n = 15)</td>
<td>CR + CRi: 72% (11/15)</td>
</tr>
</tbody>
</table>

CR = complete response, R/R = relapsed/refractory, RR = response rate

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### Selected Developmental Therapeutics in MDS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Proposed Mechanism</th>
<th>Stage of Development</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofarabine (Clolar™)</td>
<td>Halogenated nucleoside analog</td>
<td>Phase II/III (FDA approved for pediatric ALL)</td>
<td>Genzyme</td>
</tr>
<tr>
<td>ON 01910.Na (Eribynos™)</td>
<td>PI3K inhibitor/mitotic inhibitor</td>
<td>Phase VII</td>
<td>Onconova</td>
</tr>
<tr>
<td>TLK199/ezatiostat (Telintra™)</td>
<td>Glutathione analog/JNK activator</td>
<td>Phase III</td>
<td>Telik</td>
</tr>
<tr>
<td>Sapacitabine/CYC-682</td>
<td>Deoxycytidine analog -&gt; single-stranded DNA breakage, G2M arrest</td>
<td>Phase II</td>
<td>Cyclacel</td>
</tr>
<tr>
<td>Alemtuzumab (Campath™)</td>
<td>Anti-CD52 monoclonal antibody</td>
<td>Phase II (FDA approved for CLL)</td>
<td>Genzyme</td>
</tr>
<tr>
<td>HDAC inhibitors</td>
<td>Lysine deacetylase inhibition</td>
<td>Various</td>
<td>Various</td>
</tr>
</tbody>
</table>
**IV Clofarabine in MDS: Results**

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=58)</th>
<th>15 mg/m² dose (n=37)</th>
<th>30 mg/m² dose (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any response</td>
<td>21 (36%)</td>
<td>15 (41%)</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>CR (%)</td>
<td>15 (26%)</td>
<td>10 (27%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>HI (%)</td>
<td>6 (10%)</td>
<td>5 (14%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Died by 8 weeks</td>
<td>11 (19%)</td>
<td>5 (14%)</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>Alive at one year</td>
<td>37%</td>
<td>37%</td>
<td>38%</td>
</tr>
</tbody>
</table>

*Jabbour E et al. ASCO 2010; abstract 6504*

**Phase I Study of Oral TLK199 (Ezatiostat) in MDS**

- n=45, IPSS Low to INT-2, median age 71
- Starting dose 200 mg
- Up to 6,000 mg/day ezatiostat divided into 2 doses days 1-7 out of 21-day cycle was tolerated, without a DLT
- 17/45 (38%) had His by IWG 2000, most (11) at higher end of dose range (≥ 4 g/day)
- 6/29 HI-E, 4/19 HI-N, 7/21 HI-P
- Adverse events (all grade ½):
  - nausea (65%)
  - diarrhea (43%)
  - vomiting (31%)
  - constipation (13%)
  - abdominal pain (9%)

*Raza A et al. Blood 113:6533, 2009*

**Ongoing Phase II TLK199 Study**

- n=86, 36 participating centers
- Eligible: *De novo* IPSS Low/Int-1 MDS
- Endpoint: HI-E (primary)
- Schedule 1: Ezatiostat 4500 mg/day in 2 divided doses PO for 2 weeks on, 1 week off
- Schedule 2: Ezatiostat 4500 mg/day in 2 divided doses PO for 3 weeks on, 1 week off
- Clinicaltrials.gov identifier NCT00700206
ON 01910.Na- a “multikinase inhibitor”

- Ongoing studies – NIH (9) and St Vincents (6)
- 15 pts with treatment-refractory IPSS Int-1 to High risk MDS or AML (2 AML; 7 with trisomy 8)
- (13 pts at St Vincents reported in another abstract)
- Escalating doses:
  - 800 mg/m2/day over 48 hours continuous IV 3 weeks out of 4 up to
  - 1500 mg/m2/day over 48 hours continuous IV 3 weeks out of 4
- Most common AEs: cytopenias, nausea, fatigue
- Responses:
  - StV: One patient RBC transfusion-independent x 14 mos, one patient with neutrophil response; 2/6 pts with increased blasts reduced (2 progressed, 2 stable)
  - NIH: 1 Hi-E, 2 Hi-N, 2 bilineage responses

Sloand E et al ASH 2009 Abstract #120
Raza A et al ASH 2009 Abstract #3815

Sapacitabine in Patients With MDS and AML Aged ≥ 60 Years Refractory to DNMTi

- Arm A: 200 mg b.i.d. x 7 days q 3-4 weeks
- Arm B: 300 mg b.i.d. x 7 days q 3-4 weeks
- Arm C: 400 mg b.i.d. x 3 consecutive days/wk x 2 wks q 3-4 wks

<table>
<thead>
<tr>
<th></th>
<th>Arm A (n = 16)</th>
<th>Arm B (n = 17)</th>
<th>Arm C (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responses</td>
<td>1 CR; 2 major HI</td>
<td>5 major HI; 1 major HI</td>
<td></td>
</tr>
<tr>
<td>30-Day All-Cause Mortality</td>
<td>2 (n = 16)</td>
<td>6 (n = 16)</td>
<td>2 (n = 16)</td>
</tr>
<tr>
<td>Median Number of Cycles</td>
<td>2 (1 – &gt;9)</td>
<td>2 (1 – &gt;9)</td>
<td>2 (1 – &gt;9)</td>
</tr>
<tr>
<td>Patients Receiving ≥ 2 Cycles</td>
<td>4</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Patients Receiving ≥ 4 Cycles</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3/4 Adverse Events</td>
<td>6 (n = 16)</td>
<td>5 (n = 20)</td>
<td>6 (n = 16)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

García-Manero G et al. ASH 2009; abstract 1758.

Romiplostim in MDS

- Phase I/II
- Low Risk and Int I, 44 patients
- 300 – 1500 mcg weekly
- 40% durable platelet response
- = in baseline > and < 20K
- Median duration 22 ± 13 weeks
- 2 cases of AML
- 6 cases of reversible “blastosis”

Kantarjian et al. 2007. Blood 110:250a
### Romiplostim in patients MDS patients receiving 5-AC

<table>
<thead>
<tr>
<th>Cycle number</th>
<th>Placebo Baseline</th>
<th>Placebo Nadir</th>
<th>Romi 500 Baseline</th>
<th>Romi 500 Nadir</th>
<th>Romi 750 Baseline</th>
<th>Romi 750 Nadir</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>14</td>
<td>40</td>
<td>33</td>
<td>37</td>
<td>32</td>
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<tr>
<td>2</td>
<td>48</td>
<td>16</td>
<td>32</td>
<td>121</td>
<td>63</td>
<td>53</td>
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<tr>
<td>3</td>
<td>54</td>
<td>33</td>
<td>73</td>
<td>43</td>
<td>222</td>
<td>116</td>
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<tr>
<td>4</td>
<td>88</td>
<td>40</td>
<td>60</td>
<td>53</td>
<td>315</td>
<td>91</td>
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Kantarjian Blood 2008, 112: 224a