Safety and Efficacy of Combination Therapies with Azacitidine in Elderly Patients with AML or MDS

Presentations discussed in this issue:

Sekeres MA et al. Final results from a Phase I combination study of lenalidomide and azacitidine in patients with higher-risk myelodysplastic syndrome. *Blood* 2008;112; Abstract 221.

Raffoux E et al. Epigenetic therapy with azacitidine, valproic acid, and ATRA in patients with high risk AML or MDS: Results of the French VIVEDEP Phase II study. *Blood* 2008;112; Abstract 763.

Slides from presentations at ASH 2008

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**Final Results From a Phase I Combination Study of Lenalidomide and Azacitidine in Patients with Higher-Risk Myelodysplastic Syndromes (MDS)**

**Sekeres MA et al.**  
*Blood* 2008;112:Abstract 221.
Introduction

- Current standard therapy for IPSS intermediate-1-, intermediate-2-, and high-risk MDS is single agent hypomethylating agent such as azacitidine.
- Lenalidomide is the standard of care for del (5q) MDS.
- Lenalidomide also has activity in non-del (5q) MDS (Blood 2008;111:86)
- Combining azacitidine and lenalidomide has potential to improve outcomes in higher risk MDS when compared to either agent alone.

**Study objectives:**
- Safety of combination therapy with lenalidomide and azacitidine in patients with higher risk MDS
- Efficacy of combination therapy with lenalidomide and azacitidine in patients with higher risk MDS


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Mechanism of Action of Lenalidomide in MDS

**Lenalidomide targets malignant cells in the bone marrow microenvironment**

- Blocks Bone marrow vessels
- Stimulates Erythroid progenitors
- Prevents del 5q myelodysplastic clone
- Promotes Growth arrest
- Induces Cytolysis?
- Blocks TNF-α
- Blocks IL-2
- Blocks IFN-γ
- Stimulates NKT cells
- Stimulates T cells

Methyltransferase Inhibitor (MTI) Induced DNA Hypomethylation and Gene Activation

Azacitidine (AZA) and decitabine (DAC) are incorporated into DNA in lieu of cytosine residue
Inactivates DNA methyltransferase (DMT)
Leads to formation of newly synthesized DNA with unmethylated cytosine residues
Results in hypomethylation and transcription of previously quiescent genes

Trial Design

- Standard 3+3 Phase I design
- Patients with higher risk MDS as defined below were eligible:
  - IPSS score $\geq 1.5$ (Int-2 risk or high risk)
  - FAB subtype RAEB-1 or RAEB-2
- Six cohorts predefined in the trial

# Lenalidomide + Azacitidine: Dosing Table

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Azacitidine Schedule</th>
<th>Lenalidomide Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75 mg/m² SC days 1-5</td>
<td>5 mg PO days 1-14</td>
</tr>
<tr>
<td>2</td>
<td>75 mg/m² SC days 1-5</td>
<td>5 mg PO days 1-21</td>
</tr>
<tr>
<td>3</td>
<td>75 mg/m² SC days 1-5</td>
<td>10 mg PO days 1-21</td>
</tr>
<tr>
<td>4</td>
<td>50 mg/m² SC days 1-5, 8-12</td>
<td>5 mg PO days 1-14</td>
</tr>
<tr>
<td>5</td>
<td>50 mg/m² SC days 1-5, 8-12</td>
<td>5 mg PO days 1-21</td>
</tr>
<tr>
<td>6</td>
<td>50 mg/m² SC days 1-5, 8-12</td>
<td>10 mg PO days 1-21</td>
</tr>
</tbody>
</table>


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# Lenalidomide + Azacitidine: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (range), n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68 years (52-78)</td>
</tr>
<tr>
<td>Female/Male (n)</td>
<td>6/12</td>
</tr>
<tr>
<td>Time from Diagnosis</td>
<td>5 weeks (2-106)</td>
</tr>
<tr>
<td>Baseline:</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.9</td>
</tr>
<tr>
<td>Platelets (/mm³)</td>
<td>69,000</td>
</tr>
<tr>
<td>Absolute neutrophil count (/mm³)</td>
<td>832</td>
</tr>
<tr>
<td>Erythropoietin (IU/L)</td>
<td>95</td>
</tr>
<tr>
<td>Bone marrow blast count (%)</td>
<td>11</td>
</tr>
<tr>
<td>IPSS (n):</td>
<td></td>
</tr>
<tr>
<td>Intermediate-1 risk</td>
<td>3</td>
</tr>
<tr>
<td>Intermediate-2 risk</td>
<td>9</td>
</tr>
<tr>
<td>High risk</td>
<td>6</td>
</tr>
</tbody>
</table>

**Lenalidomide + Azacitidine: Toxicity Results**

- No dose-limiting toxicities were reached in all the dosing cohorts.
- Median absolute neutrophil count decreased 26% within the first 8 weeks.
- Median platelet count decrease was 0% (mean=24%) within the first 8 weeks.
- Cycle 2 was delayed for five patients (≤9 days) for recovery of counts or “other” reasons.


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**Lenalidomide + Azacitidine: Efficacy Results**

<table>
<thead>
<tr>
<th>Clinical Response (n=18)</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>72% (13)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>39% (7)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>6% (1)</td>
</tr>
<tr>
<td>Hematologic improvement (HI)</td>
<td>17% (3)</td>
</tr>
<tr>
<td>Bone marrow complete response</td>
<td>11% (2)</td>
</tr>
</tbody>
</table>

# Lenalidomide + Azacitidine: Go Forward Dose for Phase II Study

<table>
<thead>
<tr>
<th>Dosing Cohort</th>
<th>Aza Dose</th>
<th>Len Dose</th>
<th>IPSS Risk Group</th>
<th>Grade 3/4 Non-Heme Toxicities</th>
<th>Maximum Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75 mg/m² SC days 1-5</td>
<td>5 mg PO days 1-14</td>
<td>1 Int-1 2 Int-2</td>
<td>1</td>
<td>2 CR 1 progression</td>
</tr>
<tr>
<td>2</td>
<td>75 mg/m² SC days 1-5</td>
<td>5 mg PO days 1-21</td>
<td>2 Int-2 1 High</td>
<td>2</td>
<td>1 CR 1 PR, 1 HI</td>
</tr>
<tr>
<td>3</td>
<td>75 mg/m² SC days 1-5</td>
<td>10 mg PO days 1-21</td>
<td>1 Int-2 2 High</td>
<td>0</td>
<td>2 CR 1 SD</td>
</tr>
<tr>
<td>4</td>
<td>50 mg/m² SC days 1-5, 8-12</td>
<td>5 mg PO days 1-14</td>
<td>1 Int-1 2 Int-2</td>
<td>2</td>
<td>2 CR 1 SD</td>
</tr>
<tr>
<td>5</td>
<td>50 mg/m² SC days 1-5, 8-12</td>
<td>5 mg PO days 1-21</td>
<td>2 Int-2 1 High</td>
<td>2</td>
<td>1 HI, 1 SD 1 progression</td>
</tr>
<tr>
<td>6</td>
<td>50 mg/m² SC days 1-5, 8-12</td>
<td>10 mg PO days 1-21</td>
<td>1 Int-1 1 Int-2 1 High</td>
<td>2</td>
<td>1 HI 2 bone marrow CR</td>
</tr>
</tbody>
</table>


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## Summary and Conclusions

- The combination of azacitidine and lenalidomide has acceptable toxicity with good response rates.

- The go forward dose was established for Phase II studies.

Epigenetic Therapy With 5-Azacytidine, Valproic Acid, and ATRA in Patients With High-Risk AML or MDS: Results of the French VIVEDEP Phase II Study

Raffoux E et al.  
*Blood* 2008;112:Abstract 763.

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**Introduction**

- Azacytidine (AZA) is a validated therapy in patients with high-risk MDS, including patients with 20-30% marrow blasts.
- There is no clear standard therapy for elderly patients with AML, who are unfit to receive standard induction chemotherapy.
- Histone deacetylase (HDAC) inhibitors, including valproic acid, have shown activity in AML/MDS.
- Synergy of hypomethylating agents and HDAC inhibitors is supported by in vitro data.
- ATRA is a differentiating agent, and sensitivity to ATRA may be restored in non-APL cells through epigenetic mechanisms.

**Study objectives:**
- To assess the efficacy and safety of AZA and valproic acid (VPA) followed by ATRA treatment in patients with high-risk AML or MDS.

Phase II Multicenter Study of Combined AZA, VPA and ATRA Treatment in Patients with Higher-Risk AML or MDS

Eligibility (n=65)
- Untreated elderly (≥70 years) AML
- AML in 1st relapse (either if secondary AML or if 1st CR duration < 18 months)
- High-risk MDS (refractory anemia with excessive blasts [RAEB] or RAEBt with IPSS Int-2- or high-risk score)

AZA 75 mg/m²/day
SC days 1-7
VPA 35-50 mg/kg/day
PO days 1-7
ATRA 45 mg/m²/day
PO days 8-28
q4wks x 6 cycles


Patient Population (n=65)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>72 years (50-87)</td>
</tr>
<tr>
<td>Female/Male (n)</td>
<td>27/38</td>
</tr>
<tr>
<td>Diagnosis Group (n):</td>
<td></td>
</tr>
<tr>
<td>Untreated AML</td>
<td>42</td>
</tr>
<tr>
<td>Relapsed AML</td>
<td>13</td>
</tr>
<tr>
<td>High-Risk MDS</td>
<td>10</td>
</tr>
<tr>
<td>Median white blood cell (10⁹/L)</td>
<td>2.3</td>
</tr>
<tr>
<td>Median platelet count (10⁹/L)</td>
<td>43</td>
</tr>
<tr>
<td>Median marrow blasts (%)</td>
<td>31</td>
</tr>
<tr>
<td>Karyotype (n):</td>
<td></td>
</tr>
<tr>
<td>Standard-risk</td>
<td>28</td>
</tr>
<tr>
<td>High-risk</td>
<td>30</td>
</tr>
<tr>
<td>Failure/not done</td>
<td>7</td>
</tr>
</tbody>
</table>

## Efficacy Results

<table>
<thead>
<tr>
<th>Clinical Response (n=62)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response after 6 cycles</td>
<td>24%</td>
</tr>
<tr>
<td>Complete response</td>
<td>21%</td>
</tr>
<tr>
<td>Partial response</td>
<td>3%</td>
</tr>
<tr>
<td>Best response during study</td>
<td>29%</td>
</tr>
<tr>
<td>Complete response</td>
<td>23%</td>
</tr>
<tr>
<td>Partial response</td>
<td>6%</td>
</tr>
</tbody>
</table>


## Prognostic Factors for CR/PR And Death

<table>
<thead>
<tr>
<th></th>
<th>CR + PR (31% at 6 mos)</th>
<th>Death (31% at 6 mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 mos estimation</td>
<td>P-value</td>
</tr>
<tr>
<td>Age ≥ 70 years</td>
<td>24%</td>
<td>0.50</td>
</tr>
<tr>
<td>Female</td>
<td>25%</td>
<td>0.21</td>
</tr>
<tr>
<td>PS (WHO) ≥ 2</td>
<td>0%</td>
<td>0.10</td>
</tr>
<tr>
<td>WBC ≥ 1.5×10⁹/L</td>
<td>26%</td>
<td>0.47</td>
</tr>
<tr>
<td>Platelets &lt; 50×10⁹/L</td>
<td>19%</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Marrow blasts &gt; 30%</td>
<td>29%</td>
<td>0.44</td>
</tr>
<tr>
<td>High-risk karyotype</td>
<td>24%</td>
<td>0.52</td>
</tr>
<tr>
<td>Relapsed AML</td>
<td>31%</td>
<td>0.72</td>
</tr>
</tbody>
</table>

## Non-Hematological Adverse Events Grades 3-4

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N events</th>
<th>Mean cycle ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>76</td>
<td>2.0 ± 3.3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Septicemia</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>33</td>
<td>1.7 ± 1.4</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20</td>
<td>2.0 ± 1.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>1.0 ± 1.1</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>13</td>
<td>2.0 ± 1.4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>12</td>
<td>1.3 ± 1.4</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>10</td>
<td>2.5 ± 1.7</td>
</tr>
<tr>
<td>Subcutaneous puncture reaction</td>
<td>9</td>
<td>1.7 ± 1.9</td>
</tr>
</tbody>
</table>


## Summary and Conclusions

- Combination therapy with AZA, VPA and ATRA has a promising 25% to 30% response rate in patients with high risk AML/MDS.
- Response rates do not appear to differ by baseline cytogenetic risk, relapse status or percentage of marrow blasts.
- Future and larger studies are needed to better define the respective roles of these agents.