Introduction

• Relapsed/refractory AML and MDS have few treatment options and are associated with poor outcomes.
• A previously published phase 1/2 study of sequential azacitidine with high-dose lenalidomide in elderly, newly diagnosed AML revealed an ORR of 40% and a CR/CRi rate of 28% (Polley et al, Haematologica 2013).
• Based on its efficacy and tolerability, we designed a single-center phase 2 study for patients with relapsed AML and high-risk MDS (NCT01743859).

Methods

Objectives & Sample Size

• The primary objective was to determine the efficacy as measured by the CR/CRi rate.
• Secondary endpoints included overall response rate, response duration, PFS, OS, the number of eligible patients able to proceed to an allogeneic stem cell transplantation, and experience with toxicity in this population.
• The null hypothesis was a 15% CR/CRi rate and the alternative hypothesis was a clinically meaningful 30% CR/CRi rate. Using a Simon two-stage minimax design with significance of 0.10 and power in this population an allogeneic stem cell transplantation, and experience with toxicity.

Study Schema

Patients

• Eligible patients were >18 years old with relapsed/refractory AML or high-risk MDS (IPSS>1.0).
• Efforts were made to approximate a real-world clinical population but are associated with poor outcomes.
• Patients who relapsed after transplant, provided they relapsed after 1, 2 or 3 years from the last transplant, were included.

Results

Toleration

• 4 patients required dose reductions of lenalidomide to 25 mg: 1 occurred during cycle 1, 1 occurred during cycle 2 and 2 occurred during cycle 3.
• During their first cycle, 7 patients temporarily held lenalidomide, for a median of 9 days (3-13).
• In cycle 2, 2 patients held lenalidomide for 6 and 11 days.
• Reasons for holding included infection, rash, neutropenia, renal failure and colonic distention.

Table 1: Baseline Characteristics of Study Patients (N=29)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (range) or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>73 (18-87)</td>
</tr>
<tr>
<td>AML/MDS</td>
<td>26/3</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>8/21</td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>1 (1-2)</td>
</tr>
<tr>
<td>Secondary/Treatment-Related AML</td>
<td>13/25 (50%)</td>
</tr>
<tr>
<td>Number of prior therapies</td>
<td>1 (1-2)</td>
</tr>
<tr>
<td>Relapsed after allogenic SCT</td>
<td>7/29 (24%)</td>
</tr>
</tbody>
</table>

Cytogentic:

- Intermediate: 8 (28%)
- Normal Karyotype: 5 (17%)
- Unfavorable: 16 (52%)
- Monosomal: 7 (24%)
- Bone marrow blasts, %: 36% (6-95%)

- Molecular Abnormalities
  - FLT3 ITD/FLT3 TKD: 2 (7%)/13%
  - NPM1 mutation/FLT3 ITD^ITD haplotype: 0
  - IDH1/IDH2: 13% (27%)
  - JAK2: 27%

ELN Classification

- Favorable: 1 (3%)
- Intermediate-1: 3 (10%)
- Intermediate-2: 9 (31%)
- Adverse: 16 (55%)

CONSORT Diagram

Enrollment

- Assessed for eligibility: n=36
- Excluded: n=7
  - Screen fail (n=1)
  - Declined to participate (n=1)
  - Other reasons (n=5)

Allocation

- Enrolled: n=29
- Allocated to treatment: n=29

Follow-up

- Lost to follow-up (n=3)
  - Did not complete 1 cycle (n=7)
  - Did not complete 2 cycle (n=1)
  - Disease progression (n=6)

Analysis

- Analyzed (n=29)
  - Excluded from analysis (n=9)
    - Currently in Cycle 1 (n=2)
    - Did not complete 1 cycle (n=7)

Table 2: Suspected or Known Drug Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (47)</td>
<td>9 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>7 (23)</td>
<td>5 (17)</td>
<td>7 (23)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td>14 (47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (3%)</td>
<td>10 (33%)</td>
<td>7 (55)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>10 (33%)</td>
<td>3 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (17)</td>
<td>7 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (30)</td>
<td>1 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>9 (30)</td>
<td>1 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>9 (30)</td>
<td>1 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>7 (23)</td>
<td>1 (3%)</td>
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</tbody>
</table>

Clinical Outcomes

• The median number of cycles completed was 1 (0-4).
• Median follow up time is 9.5 weeks (1-100) for non-responders (p=0.034) (Figure 1).
• The overall response rate for evaluable patients was 55%, with 8 patients experiencing a CR/CRi/marrow CR (1 complete cytogenetic remission, 1 CR, 2 M CR, 4 PR).
• Median duration of response = 3 months (1-22) (Figure 1).
• Median OS = 11 weeks (2-100) (Figure 1).
• Median EFS = 9.5 weeks, 20 weeks for responders (Figure 2).
• Durability of responses was variable but on average was measured in weeks.
• Some patients who were not previously eligible for an allogeneic stem cell transplantation used this regimen to successfully bridge to this therapy.
• Eight additional patients will be enrolled to determine the primary efficacy objective.

Conclusions

• Sequential azacitidine with high-dose lenalidomide is reasonably well tolerated and active in patients with relapsed and refractory AML; numbers thus far are limited for high-risk MDS.
• Grade 4 related adverse events were due to cytopenias and their complications; other significant adverse events included the expected complications of fatigue, skin toxicity and gastrointestinal problems.
• The overall response rate for evaluable patients was 55%, with 8 patients experiencing a CR/CRi/marrow CR.
• Durability of responses was variable but on average was measured in weeks.
• Some patients who were not previously eligible for an allogeneic stem cell transplantation used this regimen to successfully bridge to this therapy.
• Eight additional patients will be enrolled to determine the primary efficacy objective.

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