MDS Foundation's Educational Patient-Caregiver Forum
Navigating Lower-risk MDS

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Conflict of interest disclosure

- I have no conflicts of interest to disclose

- I WILL include discussion of investigational or off-label use of a product in my presentation
Attendees… By show of Hands

• How many patients are in the audience?
• Patient caregivers or patient advocates?
• Pharmaceutical company representatives?
• None of the above?
For the patients in the audience….

• Please raise your hand if MDS was first described to you as a cancer?
Epidemiology of MDS – Surveillance, epidemiology and end results (SEER) DATA

- Captured as “cancer” – 2001
- 13,400 new cases per year
- Incidence Rate 4.7/100,000
- Male preponderance (M:F 1.5-2.0)

Zeidan AM et al. Blood Rev. 2018 (SEER data, based on the November 2017 submission)
Incidence Rates Based on a claims-based Algorithm

- Patients ≥65 years
- Incidence of 75/100,000 vs. 20/100,000 reported by SEER

Cogle CR et al. Blood 2011
Age at diagnosis and Overall Survival

Median age at diagnosis 77 years

5 year overall survival rate in MDS ~ 31%

Zeidan AM et al. Blood Rev. 2018 (SEER data, based on the November 2017 submission)
Diagnosis and Marrow Dysplasia

- Dysplastic changes in > 10% of cells
  - Peripheral cytopenias
  - Increased blasts
  - Increased ring sideroblasts

- Defining karyotype/genomic abnormality

Genomic Landscape of MDS: 944 patients

- 90% had 1 or more driver mutations (median: 3/pt, [0-12])

Haferlach et al. Leukemia 2014
Lower-Risk Myelodysplastic Syndrome

• **Lower Risk Definition??**
  
  • Prognostic scoring systems:
  
  • International prognostic scoring system (IPSS) Low-risk, Intermediate-1 risk (0-1.0)
  
  • Revised-IPSS: Very low risk, low-risk and intermediate risk (<3.5)
  
  • Morphology: MDS without excess blasts
Treatment Goals in Lower-risk MDS

• Improve blood counts and decrease transfusion requirements

• Improve quality of life and symptom burden

• Only curative option is by an allogeneic cell transplant

• Timing to initiate treatment is key ---- 2 factors: blood counts and patient symptoms
Treatment algorithm for MDS

MDS Diagnosed per WHO 2016 Criteria

Yes

Lower-Risk MDS

IPSS <1.5
IPSS-R ≤3.5

Calculate International prognostic scoring system (IPSS) and Revised IPSS (IPSS-R) Scores

IPSS >1.5
IPSS-R ≥3.5

Higher-Risk MDS

Is Anemia the main or only cytopenia?

Yes

Is Del(5q) present?

Yes

Lenalidomide or ESA (if EPO <500)

No

Best Approach is not clear; options include Hypomethylation agent (HMA), clinical trial, best supportive care or HSCT

No

Is Erythropoietin (EPO) level <500?

Yes

Erythropoietin Stimulating Agent (ESA) ≥12 weeks until treatment failure

No

Treatment Failure

Consider antithymocyte globulin ± cyclosporine; hypomethylation agent; Clinical trial; Best supportive care or Hematopoietic stem cell transplant (HSCT)

Treatment Failure of both Lenalidomide and ESA

Patient desires and suitable for bone marrow transplant, younger patient with good performance status & available stem cell donor

Yes

Initiate bone marrow transplant work up. In the meantime treat with HMA or intensive chemotherapy depending on patient age, bone marrow blast percentage and cytogenetic risk group

No

Hypomethylation agent (HMA) for ≥6 cycles OR clinical trial option

Clinical Trial option or best supportive care

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Lower-Risk MDS

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Treatment Failure

Erythropoietin (EPO) level <500?

No

Treatment Failure of both Lenalidomide and ESA

Yes

Treatment algorithm for lower-risk MDS

FDA Approved treatments in MDS

- Lenalidomide for deletion 5q MDS
- Hypomethylating agents (Azacitidine and Decitabine)

- Commonly used off-label:
  - Erythropoietin stimulating agents (erythropoietin and darbopoetin)
  - Lenalidomide for non-del(5q) MDS
  - Immunosuppressive therapy (Antithymocyte globulin (ATG) and cyclosporine)
# Erythropoietin Stimulating Agent Response Model in MDS

- Serum erythropoietin level (EPO) Level (U/L)
- Red blood cell transfusion requirements (# of units/month)

<table>
<thead>
<tr>
<th></th>
<th>High response rate 74% (n=34)</th>
<th>Intermediate response rate 23% (n=31)</th>
<th>Low response rate 7% (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPO ≤500 &amp; &lt;2U/mo</td>
<td>EPO ≤500 &amp; ≥2 U/mo</td>
<td>EPO &gt;500 &amp; ≥2 U/mo</td>
<td></td>
</tr>
<tr>
<td>EPO &gt;500 &amp; &lt;2U/mo</td>
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</table>

Lenalidomide response in Deletion 5q in MDS

Response Rate 67% of patients with deletion 5(q) MDS

Median duration of response >2 years

Lenalidomide in non-deletion 5q

Response rate 27% with non-deletion 5(q) MDS

Lenalidomide (N = 160)
- 26.9%

Prior ESAs* (n = 125)
- 32.0%

No prior ESAs (n = 35)
- 8.6%

Baseline EPO level

- ≤ 100 mU/mL (n = 40)
  - 42.5%
- 100–200 mU/mL (n = 27)
  - 33.3%
- 200–500 mU/mL (n = 27)
  - 25.9%
- > 500 mU/mL (n = 26)
  - 23.1%
- ≤ 500 mU/mL (n = 3)
  - 0%
- > 500 mU/mL (n = 32)
  - 9.4%

Significantly more patients on LEN achieved RBC-TI ≥ 8 weeks versus placebo (P < 0.001)

Conclusions 1 - 3 (For patients with anemia)

• Use erythropoietin stimulating agents (ESA’s) if serum erythropoietin <500 with low transfusion requirements

• Use lenalidomide in deletion 5q MDS upfront or after failure of ESA

• Consider using lenalidomide in non-deletion 5q MDS after failure of ESAs (Off label)

• However….
Combined Treatment with Lenalidomide and Epoetin Alfa Leads to Durable Responses in Patients with Epo-Refractory, Lower Risk Non-Deletion 5q [Del(5q)] MDS: **Final Results of the E2905 Intergroup Phase III Study** - an ECOG-ACRIN Cancer Research Group Study, Grant CA180820, and the National Cancer Institute of the National Institutes of Health

- Low/Intermediate 1 risk IPSS
- Hemoglobin <9.5 g/dl
- Unresponsive to EPO or TD ≥2 Units/mo + EPO >500mU/ml

**205 patients randomized**

- 96 patients Arm A (LEN alone)
  - 10 mg PO 21/28 days
- 99 patients Arm B (LEN + EA 60,000 U SQ/wk)
  - 14 excluded
  - Interruption in drug supply for 4 mo

**Primary endpoint:**
Major erythroid response (MER) at week 16

1) RBC-TI for ≥ 8 consecutive weeks AND a sustained ≥1 g/dL hemoglobin rise compared to mean pre-transfusion baseline value in TD patients

2) >2 g/dL rise in hemoglobin without transfusion for ≥8 consecutive weeks in non-TD patients (<4U RBC/8 wks)

Heavily transfusion dependent population with 85% of patients – received a median of 4 units/8 weeks

93% of patients received prior treatment with Epo and 18% azanucleosides.

<table>
<thead>
<tr>
<th></th>
<th>Arm A (Len alone)</th>
<th>Arm B (Len plus EA)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MER</td>
<td>11.5%</td>
<td>28.3%</td>
<td>0.004</td>
</tr>
<tr>
<td>MER if on treatment for 16 wks</td>
<td>15.6%</td>
<td>38.9%</td>
<td>0.004</td>
</tr>
<tr>
<td>Cross over MER (44 patients)</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mDOR</td>
<td>13 months</td>
<td>23.8 months</td>
<td></td>
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Conclusions: The addition of LEN to EA treatment is an effective strategy for the management of Epo-refractory patients with a potential duration of benefit extending to years.

Low-dose HMAs in LR-MDS: Treatment

- Regimens:
  - DAC 20 mg/m² IV D1-3 every 4 weeks
  - AZA 75 mg/m² IV/SC D1-3 every 4 weeks

- Response assessment by modified IWG 2006

- Between 11/2012 and 10/2015, 91 pts with LR-MDS treated and evaluable for response

- Median duration of follow-up = 14 months (range: 2-30 months)
### Low-dose Hypomethylating agents in LR-MDS: Response

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>CR</td>
<td>33 (36)</td>
</tr>
<tr>
<td>mCR</td>
<td>8 (9)</td>
</tr>
<tr>
<td>HI</td>
<td>13 (14)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td><strong>54 (59)</strong></td>
</tr>
<tr>
<td>SD</td>
<td>31 (34)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (7)</td>
</tr>
</tbody>
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- Median time to best response: 2 months (range: 1-20)
- Median number of cycles received: 9 (range: 2-32)
Sequence of therapy: Azacitidine vs LEN in Lower-risk MDS

- Lenalidomide is widely used off-label in the non-del5q setting
- NCCN clinical guidelines list LEN as a 2nd treatment option for TD anemia in lower-risk non-del 5q MDS after hypomethylating agents (HMAs)
- Led to wide use of HMAs as frontline therapy after erythroid stimulating agents (ESA) failure in LR-MDS
- Response rate to LEN after HMA failure is not known, as MDS-002 and MDS-005 excluded patients previously treated with HMAs
- Examined response rates to each drug when treatment order (LEN followed by HMA or HMA followed by LEN) differed

<table>
<thead>
<tr>
<th></th>
<th>LEN Response Rates (HI+)</th>
<th>AZA Response Rates (HI+)</th>
</tr>
</thead>
</table>
| **LEN 1st line**  
n= 80               | 20% (n=16)               | 30% (n=24)               |
| **Len 2nd line**  
n= 64               | 11% (n=7)                | 39% (n=25)               |
| **P value**       | **0.046**                | 0.20                     |

Komrojki et al. for MDS CRC ASH 2016; abstract 4322
Achievement of RBC TI was associated with a hypocellular bone marrow (cellularity < 20%); horse ATG plus cyclosporine was most effective.

For TI, only a hypocellular bone marrow remained a significant predictor of achieving RBC TI (<20% vs >20%: OR, 4.0; 95% CI, 1.2-13; P = .03).
Outcomes of IST in MDS

<table>
<thead>
<tr>
<th>Response</th>
<th>Percentage</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>11.2</td>
<td>6.5-18.4</td>
</tr>
<tr>
<td>PR</td>
<td>5.6</td>
<td>2.5-11.6</td>
</tr>
<tr>
<td>HI</td>
<td>32.0</td>
<td>24.1-41.0</td>
</tr>
<tr>
<td>SD</td>
<td>39.2</td>
<td>30.7-48.4</td>
</tr>
<tr>
<td>PD</td>
<td>12.0</td>
<td>7.1-19.3</td>
</tr>
<tr>
<td>ORR (CR+PR+HI)</td>
<td>48.8</td>
<td>39.8-57.9</td>
</tr>
<tr>
<td>TI</td>
<td>30</td>
<td>22.3-39.5</td>
</tr>
</tbody>
</table>

Median OS: 47.4 months
95% CI: 37.8-72.3 months

Treatment algorithm for lower-risk MDS

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Treatment Failure of both Lenalidomide and ESA


UT Southwestern
Simmons Cancer Center
Our patients, caregivers and patient advocates

Bone marrow transplant/Leukemia team
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