Overview of Myelodysplastic Syndromes

November 09, 2012
Kim-Hien Dao, DO, PhD

Speakers

- Kim-Hien Dao, DO, PhD – OVERVIEW
  - Oregon Health Sciences University, Portland, OR
- Gabrielle Meyers, MD – LOW RISK MDS
  - Oregon Health Sciences University, Portland, OR
- Erica Warlick, MD – HIGH RISK MDS
  - University of Minnesota Masonic Cancer Center, Minneapolis, MN
- Barbara Weinstein, RN, BSN, CCRP – LIVING WELL WITH MDS
  - National Heart, Lung & Blood Institute, Bethesda, MD

Overview of MDS

- What is MDS?
- Clinical presentation
- Diagnosis of MDS
- Risk groups and prognosis in MDS
- Recent advances in understanding MDS biology
- Treatment goals and current options
Myelodysplastic syndromes (MDS)

- A group of blood stem cell disorders characterized by:
  - ineffective blood cell production
  - increased leukemia development

- In the early to mid 1900’s, described as:
  - refractory anemia, preleukemic anemia, and smoldering leukemia

- Median age of diagnosis is >65 y/o

Incidence of MDS by age group

Known or suspected causes of MDS

- Mutagens – physical or chemical agent that changes the genetic material
  - Smoking
  - Benzenes
  - Radiation*
  - Chemotherapy*

*Therapy-related MDS (~10% of all cases of MDS)
Clinical presentation

- No symptoms
- Non-specific symptoms
- Infection, bruising, or bleeding may trigger blood tests

Long-term complications

- Bone marrow failure (low blood counts)
  - Infection
  - Anemia
  - Bleeding
- Acute myeloid leukemia transformation
  - Difficult to treat!

How do we make the diagnosis?

- Medical history
- Blood tests
- Bone marrow biopsy

Sometimes the diagnosis is made after repeating certain tests or after a period of observation.
Laboratory findings suggestive of MDS

- Blood:
  - Persistently low blood cell counts
- Bone marrow:
  - Abnormally high (or low) cell counts in the bone marrow
  - Disorderly development of blood cells
  - Increased % of immature (blast) cells
  - Chromosome rearrangements

<table>
<thead>
<tr>
<th>FAB</th>
<th>WHO</th>
<th>Dysplasia(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>5q- Syndrome RA</td>
<td>Erythroid</td>
</tr>
<tr>
<td></td>
<td>RCMD</td>
<td>2-3 lineages</td>
</tr>
<tr>
<td></td>
<td>MDS-U</td>
<td>1 lineages</td>
</tr>
<tr>
<td>RARS</td>
<td>RARS</td>
<td>Erythroid</td>
</tr>
<tr>
<td></td>
<td>RCMD-RS</td>
<td>2-3 lineages</td>
</tr>
<tr>
<td>RAEB</td>
<td>RAEB-1</td>
<td>1-3 lineages</td>
</tr>
<tr>
<td></td>
<td>RAEB-2</td>
<td>1-3 lineages</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>AML</td>
<td></td>
</tr>
<tr>
<td>CMMoL</td>
<td>CMMoL (if WBC &lt; 13,000u/l)</td>
<td></td>
</tr>
</tbody>
</table>

Prognosis

- Blood counts
- Blast counts
- CytoGENETICS
- Age, overall health of patient, transfusion dependence, etc.
- Therapy-related MDS

Prognostic scoring systems:
IPSS-R, WPSS, LR-PSS
International prognostic scoring system - CytoGENETICS

- **Very Good**: del(11q), -Y
- **Good**: Normal, del(20q), del(5q) alone and double, del(12p)
- **Intermediate**: +8, 7q-, t(17q), +19, +21, any other single or double, independent clones
- **Poor**: der(3)q21/q26, -7, double including 7q-, Complex (3 abnormalities)
- **Very Poor**: Complex (>3 abnormalities)

International prognostic scoring system - Prognostic Score Values

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>1</th>
<th>1.5</th>
<th>2.5</th>
<th>3.5</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyle</td>
<td>Very Good</td>
<td>Good</td>
<td>Int</td>
<td>Poor</td>
<td>Very Poor</td>
<td></td>
</tr>
<tr>
<td>Blasts</td>
<td>&lt;5%</td>
<td>5-10%</td>
<td>11-30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>&gt;10</td>
<td>&lt;10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleq</td>
<td>≥100</td>
<td>&lt;100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From Dr. Peter Greenberg, IWG-PM data

International prognostic scoring system - Risk groups by total points

- **Very Low**: 0 - 2
- **Good**: >2 - 3.5
- **Intermediate**: >3.5 - 5
- **High**: >5 - 6
- **Very High**: >6

For consideration of age:
(age in yrs - 70) x 0.04, add result to sum of other variables.
**Freedom from AML transformation**

- Probability:
  - Very good: Green
  - Good: Orange
  - Int: Yellow
  - Poor: Red
  - Very poor: Blue

- Time (months):
  - ~5% develop AML
  - 60% develop AML

**Survival**

- Probability:
  - Very good: Green
  - Good: Orange
  - Int: Yellow
  - Poor: Red
  - Very poor: Blue

- Time (months):
  - 80% are living
  - 8% are living

**Goals of treatment**

- Control symptoms and prevent complications from low blood counts
- Improve quality of life
- Delay disease progression (marrow failure or leukemia development)
- Improve quantity of life
- Cure
Treatment

- Supportive care (e.g., transfusions and antibiotics)
- Growth factors
- Immunosuppression
- Low intensity treatment - Thalidomide, Lenalidomide, Hypomethylating agents (Azacytidine and Decitabine)
- High dose chemotherapy
- Hematopoietic stem cell transplant

Advances in understanding MDS biology

- Epigenetic changes
- Immune system
- Cell death
- Environmental factors
- Microenvironment
- DNA damage

Adapted from Dr. Maciejewski

Epigenetic changes by DNA methylation

Normal

- CH3 = methyl groups

MDS

- CH3 = methyl groups

Azacytidine

Genes ON

- Genes that repair DNA damage
- Genes that modify DNA structure
- Genes that control differentiation
- Genes that control survival and growth

Adapted from Dr. Maciejewski
Gene mutations in MDS

Response rate to AZA
>80% vs. ~40% in patients with these mutations

Clinical trials

- Combining agents with hypomethylating agents to improve efficacy.
- Novel hypomethylating agents.
- Novel chemotherapy agents and small molecule inhibitors.
- Improve outcomes in stem cell transplant.

Clinical trials at OHSU

- Sample collection before and during treatment for research studies (ACTIVE)
  - Azacytidine, Decitabine, or Lenalidomide alone
  - Azacytidine + Lenalidomide
- Low risk MDS, target inflammatory cytokins (?2013)
- MDS, oral azacytidine inhibition (TBD)
- Refractory AML, small molecule inhibitor (ACTIVE)
Thank you! Questions?

- Kim-Hien Dao, DO, PhD – OVERVIEW
  > Oregon Health Sciences University, Portland, OR

- Gabrielle Meyers, MD – LOW RISK MDS
  > Oregon Health Sciences University, Portland, OR

- Erica Warlick, MD – HIGH RISK MDS
  > University of Minnesota Masonic Cancer Center, Minneapolis, MN

- Barbara Weinstein, RN, BSN, CCRP – LIVING WELL WITH MDS
  > National Heart, Lung & Blood Institute, Bethesda, MD