Myelodysplastic Syndromes (MDS) Basics and Lower-Risk MDS

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MDS Highlights

- Prior chemotherapy (alkylator chemotherapy, topoisomerase II inhibitors)
- Prior radiation exposure
- ~1/2 of patients have abnormalities, usually numeric anomalies
- Median age is ~70 (but can occur at any age)
- >95% of patients have cytopenias, most commonly anemia
- Bone marrow usually hypercellular, cells look abnormal (“dysplastic”), blasts may be increased
- Infection, bleeding, complications of anemia (50%)
- MDS (25%)
- AML (25%)
- Death from other causes (25%)

>13,000 new cases per year in the US

85% of patients have no known exposures

>10% of patients have abnormal chromosomes, usually numeric anomalies

85% of patients have no known exposures

≥20% marrow “blasts”

MDS is in here – in the "shadowlands" between cancer and not cancer

Hematologic Malignancy

- Myeloid Cancer
  - Chronic Myeloid Disorders
  - Acute Myeloid Leukemia
    - 20% marrow “blasts”
  - MDS is in here – in the "shadowlands" between cancer and not cancer
- Lymphoid Cancer
  - Lymphoma (Hodgkin, NHL)
  - Plasma Cell Disorders (Myeloma)
  - Acute Lymphoid Leukemia
International Prognostic Scoring System version 1.0 (1997)

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score 0</th>
<th>Score 0.5</th>
<th>Score 1.0</th>
<th>Score 1.5</th>
<th>Score 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blasts (%)</td>
<td>&lt;5%</td>
<td>5-10%</td>
<td>---</td>
<td>11-20%</td>
<td>&gt;20%</td>
</tr>
<tr>
<td>Karyotype class*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td># of cytopenias**</td>
<td>0 or 1</td>
<td>2 or 3</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

*Karyotypes: Good = normal, -Y, del(5q) alone, del(20q) alone; Poor = chromosome 7 abnormalities or complex; Intermediate = other karyotypes

**Cytopenias: Hb < 10 g/dL, ANC <1800/uL, platelets <100,000/uL


IPSS Risk Categories: Patient Distribution And Outcomes

<table>
<thead>
<tr>
<th>Score sum</th>
<th>IPSS Risk Category</th>
<th>Median survival for over age 60 group (years)</th>
<th>Time until 25% get AML (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>Int-1</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>Int-2</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>&gt;=2.5</td>
<td>High</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Honestly, we really don’t know who is truly “lower risk”...


Death

(IFS 1997; n=816)

... even with improved lower-risk-specific scoring systems.


Additional “extra-IPSS” cytogenetic (chromosome) information can be helpful...

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Karyotypes (22 groups)</th>
<th>Median survival (months)</th>
<th>Time until 25% of patients developed AML (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>5q-, 12p-, 20q-, +21, Y, 11q, (11p23), normal, any 2 abnormalities including 5q-</td>
<td>51</td>
<td>71.9</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>+1q, 3q21, +q abnormalities, +8, 17q; +19-21, any other single abnormality not including abnormalities of chromosomes 5q or 7</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>X-, 7 or 7q, any double abnormality with 7 or 7q, complex with 3 abnormalities</td>
<td>15.6</td>
<td>6</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>Complex with ≥3 abnormalities</td>
<td>5.9</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Schanz J et al - ASH 2009, Abstract #2772
... as can molecular genetic information (rarely available) ...

... and general health matters, too.

Bejar R et al, manuscript submitted (ASH 2010 Abstract #300)

Naqvi K et al, ASH 2010, Abstract #605
Outline: Treatments

- Review current treatment pathways (NCCN guidelines)
- Hematopoietic growth factors
  - Erythropoiesis stimulating agents (ESAs), epoetin and darbepoetin
  - Thrombopoiesis stimulating agents (TPO agonists), romiplostim and eltrombopag
- Immunomodulatory / immunosuppressive therapy
  - Lenalidomide
  - ATG/cyclosporine etc
- Iron chelation therapy, pros and cons

Medications Currently Commonly Used for Patients with MDS

<table>
<thead>
<tr>
<th>FDA Approved for MDS-Related Indications</th>
<th>FDA Approved for Other Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomethylating agents / DNA methyltransferase inhibitors / epigenetic drugs</td>
<td>Blood cell (hematopoietic) growth factors</td>
</tr>
<tr>
<td>Azacitidine (Vidaza ®) Approved May 2004</td>
<td>Red cell growth factors</td>
</tr>
<tr>
<td>Decitabine (Dacogen ®) Approved May 2006</td>
<td>Epoetin alfa (Procrit ®)</td>
</tr>
<tr>
<td>Immunomodulatory drug (iMiD)</td>
<td>Darbepoetin alfa (Aranesp ®)</td>
</tr>
<tr>
<td>Lenalidomide (Revlimid ®) Approved December 2005</td>
<td>White cell growth factors</td>
</tr>
<tr>
<td>Iron chelators</td>
<td>Filgrastim, G-CSF (Neupogen ®)</td>
</tr>
<tr>
<td>Deferasirox (Exjade ®) Approved November 2005</td>
<td>Pegfilgrastim (Neulasta ®)</td>
</tr>
<tr>
<td>Deferoxamine (Desferal ®) Approved 1968</td>
<td>Platelet growth factors</td>
</tr>
<tr>
<td></td>
<td>Romiplostim (NPlate ®)</td>
</tr>
<tr>
<td></td>
<td>Eltrombopag (Promacta ®)</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressive drugs</td>
</tr>
</tbody>
</table>

Thalidomide, androgens, other biologics

Chemotherapy or stem cell transplant

NCCN guidelines: lower-risk MDS (IPSS Low/Intermediate-1 Risk Groups)

Based on v.2 2011; www.nccn.org
Hematopoietic growth factors

Response Prediction For Erythropoietin In MDS

<table>
<thead>
<tr>
<th>Total Score</th>
<th>IWG Erythroid Response (patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good</strong>: &gt;+1</td>
<td>74% (n=34)</td>
</tr>
<tr>
<td><strong>Intermediate</strong>: -1 to +1</td>
<td>23% (n=31)</td>
</tr>
<tr>
<td><strong>Poor</strong>: &lt;-1</td>
<td>7% (n=39)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum EPO (U/L)</th>
<th>Transfusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 = +2 pts</td>
<td>&lt;2 Units/month = +2 pts</td>
</tr>
<tr>
<td>100-500 = +1 pt</td>
<td>&gt;=2 Units/month = -2 pts</td>
</tr>
<tr>
<td>&gt;500 = -3 pts</td>
<td></td>
</tr>
</tbody>
</table>

Response = >1.5 g/dL Hb increment or transfusion independence

Redrawn from Hellstrom-Lindberg E et al Br J Haem 2003; 120:1037

New ESA APPRISE “REMS” Program

- FDA-mandated “Risk Evaluation and Management System”
- Went into full effect January 24, 2011
- Applies to all Erythropoiesis Stimulating Agent (ESA) prescriptions except renal failure - hemodialysis
- Requires signing a form about risks in patients with cancer (solid tumors)
What if you don’t respond to ESAs?

177 patients treated with ESAs (1998-2006)
94 with “primary” resistance
83 with relapse after initial IWG 2000 response

Age >75 yrs and adverse cytogenetics predictive of shorter survival in resistant, but not relapsed patients

Comparing these patients to 226 responding to ESAs, lack of response did NOT predict for worse survival or AML transformation.

Kelaidi et al. Blood 2010;116:442a

The Other Growth Factor: Thrombopoietin (TPO)

Romiplostim (NPlate)

Fenaux et al. Blood 2010;116: abstract 1885a

The Other Growth Factor: Thrombopoietin - the dark side?

AML Progression and Blast Increases

- Three cases of progression to AML were reported, corresponding to an annual on-study event rate of 5.5% (95% CI: 2% to 18%), based on a parametric regression model
- Peripheral blasts were increased in 2 other patients (MDS-U and RA at baseline) and disappeared in both cases after romiplostim discontinuation

Fenaux et al. Blood 2010;116: abstract 1885a
Immunomodulatory and immunosuppressive therapy

Steensma 2008

Anti-Thymocyte Globulin (ATG) ± Cyclosporine in MDS

- 21/61 (34%) free of transfusions in NIH study, 10/21 (48%) increased platelet counts
- No responses in Mayo study
- Rabbit=horse?
- Putative markers of likely responders:
  - HLA-DR15+
  - Younger age
  - Low transfusion needs
  - PNH clone
  - Trisomy 8 or normal chromosomes
  - Low marrow cellularity
Bone Marrow Failure Consortium
MDS ATG study

Eligibility:
MDS (not CMML) with Hb <9 g/dL, ANC <1.0 x 10^9/L, or platelets <50 x 10^9/L
<10% marrow blasts and adequate organ function

Regimen: Rabbit ATG (rATG, Thymoglobulin®) 2.5 mg/kg/day IV x 4 days

Primary endpoint: Overall response rate (IWG 2000 criteria)

Enrolled patients: 39 enrolled over 6 years, but only 21 evaluable
Use of other therapy, n=5
Found to be ineligible, n=7
Died before first dose, n=2
Non-adherence, n=1
Otherwise not evaluable, n=3

Epling-Burnette PK et al, ASH 2010 Abstract #602

Bone Marrow Failure Consortium
MDS ATG study results

Evaluable patients:
- Median age 66 years (range, 44-79)
- 6 IPSS low-risk, 12 IPSS Int-1, 3 IPSS Int-2

No CR/PRs
9/21 (43%) patients with hematological improvement
- Median time to response: 75 days (range, 3 days-3.7 months)
- Median duration of response: 7.2 months (range, 2-22+ months)
- 3 deaths from infection

Correlates of response:
- Only 4 patients had HLA DR15; 3 responded
- No correlation: IPSS, cytopenias, LDH, karyotype, age-adjusted bone marrow cellularity, and M:E ratio
- Responders were: 8 months from diagnosis
- Non-responders were: 42 months from diagnosis (p=0.18)

Epling-Burnette PK et al, ASH 2010 Abstract #602

Lenalidomide development history
in MDS

MDS-001
N = 43
Phase I/II initiated Feb 2002
List A et al NEJM 2005

Del(5q)

MDS-003
N = 148
Phase II initiated July 2003
List A et al NEJM 2006

67% transfusion independence
Median duration of response >2 years
45% complete cytogenetic remission

Non-del(5q)

MDS-002
N = 214
Phase II initiated July 2003
Raza A et al Blood 2008

67% transfusion independence
Median duration of response >2 years
9% complete cytogenetic remission

62% transfusion independence
Median duration of response 41 weeks
26% complete cytogenetic remission
Lenalidomide MDS-005 study (ongoing)

- **n=375 pts**
- **Key Eligibility:**
  - IPSS Low/Int-1 MDS
  - non-del(5q)
  - RBC transfusion requiring
  - No ESA response or high serum EPO level

**Primary endpoint:**
Transfusion independence

**Iron Chelation**

**Incidence of RBC Transfusion Dependence In MDS**

<table>
<thead>
<tr>
<th>IPSS Category</th>
<th>Proportion RBC Transfusion Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>39%</td>
</tr>
<tr>
<td>Intermediate-1 Risk</td>
<td>50%</td>
</tr>
<tr>
<td>Intermediate-2 Risk</td>
<td>63%</td>
</tr>
<tr>
<td>High Risk</td>
<td>79%</td>
</tr>
</tbody>
</table>

Brechignac S et al Blood 2004 104;236b (abstract 4716)
Blood Transfusions: The Good…

• Improves “oxygen carrying capacity” of blood
• Improves patients’ ability to function
• RBCs can be given more or less indefinitely
• In AA/MDS, the “backup” when other treatments fail
• Benefit for donors: sense of altruism

… and the Bad

• Time-consuming
• Costly
• Small but real infection risk and associated fears
• Risk of transfusion reaction (febrile, allergic)
• Alloimmunization
• Each unit of blood carries ~250 mg elemental iron

The Risk Of Transfusion Dependence In MDS

Cumulative Probability of Survival among 374 MDS Patients at Pavia, Italy, 1992–2002 (transfusion hazard ratio for death, 1.58; P=0.005).

**Diagnosis of Iron Overload**

Liver biopsy

R2* MRI (Ferriscan™)

SEROLOGY

Liver

Ferritin Transferrin Sat.

Normal

Moderate iron overload

Mild iron overload

Heavy iron overload

**Correlation between ferritin and poorer outcome in lower-risk MDS**

RA/RARS/sq- syndrome

$p<0.001$

RCMD/RCMD-RS

$p=0.07$

Based on 426 patients evaluated in Pavia, Italy

Malcovati L. Leukemia Research 31S3 (2007) S2–S6

**Iron Chelation Options in the US**

Deferasirox (Exjade™)

Injectable – 8 to 12 hours overnight 5-7 nights per week

Deferoxamine (Desferal™)

Oral – once daily
### Chelation Clinical Guidelines

- Many organizations have guidelines for iron monitoring and iron chelation in MDS
  - At least 8 different guidelines in the last 10 years
  - Only partially evidence-based
- In general, these guidelines suggest:
  - **Periodic serum ferritin monitoring**, supplemented by other techniques for assessing iron burden
  - Consideration of iron chelation when patient has **persistent ferritin >1000 ng/mL** or other evidence of iron overload such as MRI, and lower-risk MDS
  - Start thinking about iron overload after 20-50 units RBCs

### Study Design: US03 Exjade Study

_n=176_

<table>
<thead>
<tr>
<th>Time of analysis</th>
<th>Treatment initiated</th>
<th>4-week screening period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core phase</td>
<td>Daily deferasirox</td>
<td>BL</td>
</tr>
<tr>
<td>Extension phase</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feltin BL</th>
<th>Safety BL</th>
<th>LPI BL</th>
<th>Timepoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>5</td>
<td>9</td>
<td>every 4 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Remember What Happened to Folate…

**Homocysteine** → **Heart Disease**

**THEREFORE…**

**Folate** → **Homocysteine** → **Heart Disease**

**BUT…**

**Folate** → **Homocysteine** → **Survival and Heart Disease**


And now **Iron** in MDS?…

**Iron** → **End Organ Damage**

**THEREFORE…**

**Chelation** → **Iron** → **End Organ Damage**

**BUT…**

**Chelation** → **Iron** → ??????????

Thank you!