Myelodysplastic Syndromes: Current Thinking on the Disease, Diagnosis, and Treatment

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Introduction

• Group of malignant hematopoietic stem cell disorders
  – Atypical appearing cells (cytologic dysplasia)
  – Ineffective differentiation/maturation
  – Low peripheral blood counts

• Variably increased risk of progression to acute myeloid leukemia (AML)

Epidemiology


Epidemiology

• Median Age ~70
• Age-adjusted annual incidence rate of MDS in the US: 3.3 per 100,000 people\(^1\) (~10,000 new cases/year)
• Slight male predominance, except del(5q)
  – 25% to 30% of recently diagnosed patients with higher-risk MDS\(^2\)
• Few RF identified: exposure to chemicals, radiation, tobacco, or chemotherapy, genetic abnormalities

Signs/Symptoms

• Discovered incidentally or after a blood count is drawn due to symptoms, including:
  – fatigue (anemia)
  – infections (neutropenia)
  – bleeding (thrombocytopenia)

• Cytopenias:
  – Anemia, often macrocytic: ~85%
  – Neutropenia: ~50%
  – Thrombocytopenia: 67%\(^1\)
  • Platelets <50 k/dL: 43%


Diagnosis

Review of peripheral blood smear can be helpful

Normal Neutrophil

Dysplastic Neutrophil

Blast with Auer Rod

1. Rollison DE, Blood. 2008
2. Sekeres MA, JNCI 2008
Diagnosis

* Bone marrow biopsy and aspirate is **essential** to establish the diagnosis, determine the subtype, and risk-stratify

- Morphologic evaluation
- Chromosome analysis (karyotype)
- Flow cytometry – detect cells with abnormal phenotype
- Mutational analysis

Mimics/Things to Rule Out

- B12/folate deficiency
- Copper deficiency
- Alcoholism
- Chemotherapy
- HIV, especially while on HAART
- Use of growth factors such as G-CSF (Neupogen)

Disease Overlap

- PNH
- LGL
- MDS
- AA
- MPN

Case

56 yo F p/w 4-week history of fatigue, nausea, sweating and fevers. She is slightly lightheaded with some shortness of breath. She has had a poor appetite but no weight loss.

- **Past Medical History:** Migraine headaches, hypertension, h/o dental abscess
- **Medications:** prn Tylenol, folic acid
- **Family History:** no full siblings

Laboratory Evaluation:

- White blood cells 5.9 (4.5-11 K/mcL)
- Absolute neutrophil count: 3.8 (1.7-7.3 K/mcL)
- Hemoglobin **8.4** (11.9-15.8 g/dL)
- Hematocrit **28.8** (35-45%)
- Platelets **58** (160-370 K/mcL)
- HIV, Hep C, B12, folate are all negative or normal
Case
Bone marrow biopsy and aspirate:
• Hypercellular (90%) with atypical megakaryocytes and neutrophils, with no increase in blasts (<2%). Findings are consistent with myelodysplastic syndrome (refractory cytopenia with multilineage dysplasia).
• Karyotype: 47 XX, +8 [20]

WHO Classification in 2016

<table>
<thead>
<tr>
<th>2008</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia (RCUD)</td>
<td>MDS with single lineage dysplasia (MDS-SLD)</td>
</tr>
<tr>
<td>Refractory Anemia (RA)</td>
<td>MDS with ring sideroblasts (MDS-RS)</td>
</tr>
<tr>
<td>Refractory Neutropenia (RN)</td>
<td>MDS with ring sideroblasts (MDS-RS)</td>
</tr>
<tr>
<td>Refractory Thrombocytopenia (RT)</td>
<td>MDS with ring sideroblasts (MDS-RS-MLD)</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>MDS with isolated del(5q)</td>
</tr>
<tr>
<td>MDS with isolated del(20q)</td>
<td>MDS with excess blasts (MDS-MDS)</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-1 (RAEB-1)</td>
<td>MDS with excess blasts-1 (MDS-EB-1)</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
<td>MDS with excess blasts-2 (MDS-EB-2)</td>
</tr>
<tr>
<td>MDS – unclassified (MDS-U)</td>
<td>MDS, unclassifiable (MDS-U)</td>
</tr>
</tbody>
</table>

WHO Classification Based System

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT category</td>
<td>RA, RA-U, Sq</td>
<td>RCMD, RCMD-RS</td>
<td>RAEB-1</td>
<td>RAEB-2</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>---</td>
</tr>
<tr>
<td>Transfusion requirement</td>
<td>No</td>
<td>Regular</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Prognostic Factor | Points
--- | ---
Performance Status | 2
Age, y | 1
18-60 | 1
60-64 | 1
65 | 2
Platelets, x 10^9/L | 1
30-49 | 2
<30 | 3
Hemoglobin (g/dL) | 1
<12 | 2
<10 | 3
Bone Marrow Blasts, % | 1
5-10 | 1
10-20 | 3
WBC > 20 x 10^9/L | 3
Karyotype: chromosome 7 abnormal | 3
Poor Transfusion, yes | 1

International Prognostic Scoring System

<table>
<thead>
<tr>
<th>BM blasts (%)</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0 / 1</td>
<td>2 / 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Global MD Anderson Risk Model

<table>
<thead>
<tr>
<th>Score</th>
<th>Median OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low: 0-4</td>
<td>54</td>
</tr>
<tr>
<td>Int: 5-9</td>
<td>25</td>
</tr>
<tr>
<td>High: ≥ 10</td>
<td>14</td>
</tr>
</tbody>
</table>

Malcovati L, et al. JCO 2007;25:3503-3510
Greenberg P et al, Blood 1997; 89:2079-88
Kantarjian H.  Cancer 2008; 113:1201-41
Revised IPSS

<table>
<thead>
<tr>
<th>Prognostic Subgroup</th>
<th>Prognostic variable</th>
<th>Median Survival, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Good</td>
<td>-1, del(11q)</td>
<td>5.4</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(5q), del(13q), del(20q), double including del(5q)</td>
<td>4.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>del(17q), +8, +19, +17q, any other single or double independent clones</td>
<td>2.7</td>
</tr>
<tr>
<td>Poor</td>
<td>-7, inv(3)(12q)/del(3q), double including 7q, del(7q), complex: 3 abnormalities</td>
<td>1.5</td>
</tr>
<tr>
<td>Very Poor</td>
<td>Complex: &gt; 3 abnormalities</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Prognostic variable: 0, 0.5, 1, 1.5, 2, 3, 4, 5

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>&gt; 1.5</td>
</tr>
<tr>
<td>Low</td>
<td>&gt; 1.5 - 3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt; 3 - 4.5</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 4.5 - 6</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt; 6</td>
</tr>
</tbody>
</table>

Point Mutations in MDS

- >90% of patients with MDS have at least 1 somatic mutation
- Some have independent prognostic value

Lower-Risk Disease

- Observation
- Growth Factors
- Immunosuppressive Therapy
- Lenalidomide
- Hypomethylating Agents
- Clinical Trial

Observation

- Not all patients need active therapy for MDS
  - Mild peripheral blood abnormalities
  - No need for transfusions
  - Asymptomatic

- Treating lower-risk patients early has not been shown to improve outcomes

Erythropoiesis Stimulating Agents ± G-CSF

- 30-40% response rates in various studies
- Epoetin alfa and darbepoetin are likely as effective
Growth Factors

<table>
<thead>
<tr>
<th>Score</th>
<th>RA, RARS, RAEB</th>
<th>Score = -1 to +1</th>
<th>Score &gt; +1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (7%)</td>
<td></td>
<td>Intermediate (23%)</td>
<td>Good (74%)</td>
</tr>
</tbody>
</table>

Serum EPO (U/l)

- <100: +2
- 100-500: +1
- >500: -3

RBC Transfusions

- <2 units/m: +2
- ≥ 2 units/m: -2

Modified from: Hellstrom-Lindberg E, BJH 2003

Caution with ESAs

- In some studies in patients with solid tumors receiving chemotherapy, ESAs have been linked to increased heart attacks, stroke, blood clots, tumor growth, and death
- This HAS NOT been shown in patients with MDS

ATG & Cyclosporine

- ATG with cyclosporine vs. best supportive care
  - low- to intermediate-risk pts with < 10% blasts
  - transfusion dependent < 24 months
- Increased hematologic response rates by 6 months (29% vs. 9%)
  - Median duration of response 16.4 months

Immunosuppressive Therapy

Favorable factors for response:
- Age
- Immune receptor type (HLA-DR15)
- Hypocellular marrow
- PNH clones
- Low CD4:CD8 ratio

Lenalidomide – Phase I Study

- 43 patients with lower-risk MDS and symptomatic or transfusion-dependent anemia
- 24/43 patients responded (56%)
  - 10/12 patients with del5q responded (83%)

MDS with isolated del(5q)

- 10-15% of patients with MDS
- Presentation:
  - Normal or increased megakaryocytes in the bone marrow
  - <5% blasts in the bone marrow
  - Anemia with normal or elevated platelets in PB
- Female predominance
- Low risk of progression

List AF et al, NEJM 2003

Passweg JR, JCO 2010

Passweg JR, JCO 2010
Phase III study: MDS-004

- Primary endpoint: RBC-TI ≥ 26 consecutive weeks

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lenalidomide 5 mg</th>
<th>Lenalidomide 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>nITT population</td>
<td>n = 51</td>
<td>n = 47</td>
<td>n = 47</td>
</tr>
<tr>
<td>Protocol defined (≥ 36 weeks)</td>
<td>3 (5.0) [1.2-16.2]</td>
<td>20 [42.6] [20.3-37.8]^*</td>
<td>23 [56.1] [38.7-71.5]^*</td>
</tr>
<tr>
<td>SWOG 2004 (≤ 1 week)</td>
<td>4 (7.0) [2.2-18.0]</td>
<td>24 [41.3] [16.6-61.9]^*</td>
<td>25 [56.1] [44.3-75.8]^*</td>
</tr>
<tr>
<td>SWOG 2004 (≥ 1 week)</td>
<td>3 (5.0) [1.2-16.2]</td>
<td>24 [41.3] [16.6-61.9]^*</td>
<td>25 [56.1] [44.3-75.8]^*</td>
</tr>
</tbody>
</table>

- Crossover allowed, but no improvement in survival seen

Fenaux P. Blood 2011

Lenalidomide Side Effects

- Neutropenia, thrombocytopenia – may require dose interruption/reduction
- Dry skin, rash, itching (esp. scalp)
- Diarrhea (esp. lactose intolerant patients)
- Muscle cramps
- Fatigue
- Rare: hypothyroidism, hypogonadism, deep venous thrombosis (blood clot)

All are generally manageable, most decrease with time and usually do not require permanent discontinuation

HMAs in lower-risk patients

- 151 patients (63% RA or RARS) randomly assigned to 1 of 3 different weekend-sparing AZA regimens

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>AZA 5 mg/day</th>
<th>AZA 10 mg/day</th>
<th>AZA 20 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>51</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Grade 3/4 toxicity</td>
<td>84%, 77%, and 58%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marrow response and survival NOT evaluated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lyons RJ et al. JCO 2009; 27:1850-1856

Iron Balance

- Daily intake: 1-2 mg
- Daily losses: 1-2 mg
- Iron chelation therapy: 250 mg/unit

- Long-term complications:
  - Heart failure
  - Liver disease
  - Diabetes
  - Skin changes
  - Endocrine dysfunction

Iron Chelation Therapy

- Transfusion dependence and elevated ferritin correlate with poorer outcomes
- Deferasirox decreases serum ferritin and labile plasma iron, but high discontinuation rates (up to 80%)1,2
- Consider:
  - Lower-risk disease with long life expectancy
  - Serum ferritin greater than 1,000-2,500 mcg/L or other clinical evidence of iron overload

1. Lai AF et al. JCO 2012;30:2134-9
Our Patient

• Risk Score
  – IPSS: Intermediate-1
  – MDACC score: Low
  – IPSS-R: Intermediate
• Was not heavily transfusion dependent and was therefore started on darbepoetin
• Hemoglobin did not improve after 16 weeks of treatment, and she began needing more pRBC transfusions

Our Patient

White blood cells 1.9 (4.5-11 K/mcL)
- Absolute neutrophil count: 0.3 (1.7-7.3 K/mcL)
- 2% blasts
Hemoglobin 8.1 (11.9-15.8 g/dL)
Hematocrit 28.8% (35-45%)
Platelets 41 (160-370 K/mcL)

Our Patient

Bone marrow biopsy and aspirate:
• Hypercellular (90%) with trilineage dysplasia, with mildly increased blasts (7%), consistent with progression of MDS to refractory anemia with excess blasts-1.
• Karyotype: 47 XX, +8 [20]

Hypomethylating Agents

5-azacitidine
N2H3
- Affects RNA metabolism and protein synthesis
- Can be converted to deoxyribonucleoside and inhibit DNA synthesis or DNA methyltransferase

Decitabine
N2H3
- Inhibits DNA synthesis and covalently (N3) DNA
- Higher demethylating activity
- Crosslinks DNA at high doses

DNA Methylation

CpG Island
Exon 1
DNMT3a
Hypomethylation

CpG Island
Exon 1
HaMe
Hypermethylation

TET2
α-KG
isocitrate

IDH1/2
Decitabine vs. Best Supportive Care

2 Phase III trials:

1) IPSS ≥ 0.5 (Intermediate 1 or higher)

<table>
<thead>
<tr>
<th></th>
<th>Decitabine, n=89</th>
<th>BSC, n=81</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>17% (9% CR)</td>
<td>0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>14.0 months</td>
<td>14.9 months</td>
<td>0.636</td>
</tr>
</tbody>
</table>

2) Elderly patients with higher-risk MDS

<table>
<thead>
<tr>
<th></th>
<th>Decitabine, n=119</th>
<th>BSC, n=114</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>34% (13% CR)</td>
<td>2%</td>
<td>NR</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>10.1 months</td>
<td>8.5 months</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Decitabine was NOT continued until disease progression

1. Kantarjian H, Cancer 2006
2. Lubbert M, JCO 2011

Azacitidine

• CALGB 9221: Phase III trial of Azacitidine vs. supportive care
  – Any FAB category
  – IPSS was only available for 81 patients (42%)
  – Crossover allowed after at least 4 months on supportive care arm

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Azacitidine, n=99</th>
<th>BSC, n=92</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>60% (23% CR+PR)</td>
<td>5% (0 CR or PR)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to AML/death</td>
<td>21 months</td>
<td>13 months</td>
<td>0.007</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>20 months</td>
<td>14 months</td>
<td>0.10</td>
</tr>
</tbody>
</table>

AZA-001: Azacitidine vs. CCR

Physician choice of 1 of 3 CCRs
1. Best Supportive Care only
2. LDAC (20 mg/m²/day SC x 14 day q28-42 days)
3. 7 + 3 chemotherapy (induction + 1-2 consolidation cycles)

Stratified by
• FAB: RAEB, RAEB-T
• IPSS: int-2, high

Treatment continued until unacceptable toxicity or AML transformation or disease progression


AZA-001: Azacitidine vs. CCR

HR: 0.58 (95% CI: 0.43-0.77; log rank P = .0001)

ORR 29% (17% CR) in azacitidine arm vs. 12% (8% CR) in CCR arm


Azacitidine – Other Issues

• Median cycles to 1st response: 2-3\(^1,2\)
• Responders must continue treatment indefinitely
• Do NOT need a complete response to benefit\(^3\)
  – OS benefit in AZA-001 trial was maintained even if CR patients were excluded
• Side effects: Decreased blood counts, nausea, constipation, fatigue, infections
  – Usually manageable without discontinuation of drug

1. Silverman LR, JCO 2006
2. Silverman LR, Cancer 2011
3. List AF, ASCO 2006; Abstract #7006

Our Patient

• Was started on azacitidine and referred for a transplant consultation.
• After 4 cycles her counts had not changed
• Repeat bone marrow biopsy:
  – Over 95% cellular with persistent trilineage dysplasia and increased blasts from 7% previously to 13% (RAEB-2)
Outcomes after HMA Failure

### MDS & CMML Patients

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. of Patients Treated</th>
<th>No. of HMA failures</th>
<th>AML Progression</th>
<th>Median OS (months)</th>
<th>OS at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC¹</td>
<td>NR</td>
<td>87</td>
<td>25 (29%)</td>
<td>4.3</td>
<td>30%</td>
</tr>
<tr>
<td>GFM²</td>
<td>435</td>
<td>NR</td>
<td>NR</td>
<td>5.6</td>
<td>29%</td>
</tr>
<tr>
<td>Moffitt³</td>
<td>151</td>
<td>59</td>
<td>12 (30.3%)</td>
<td>5.8</td>
<td>17%</td>
</tr>
</tbody>
</table>

2. Prébet T et al, JCO 2011; 29:3322

### Transplant in MDS

- ONLY potentially curative therapy for MDS, but is associated with significant complications
- Life Expectancy (years)

<table>
<thead>
<tr>
<th>IPSS Risk Group</th>
<th>At diagnosis</th>
<th>At AML progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>6.51</td>
<td>7.21</td>
</tr>
<tr>
<td>Int-1</td>
<td>4.61</td>
<td>5.16</td>
</tr>
<tr>
<td>Int-2</td>
<td>4.93</td>
<td>2.84</td>
</tr>
<tr>
<td>High</td>
<td>3.2</td>
<td>2.75</td>
</tr>
</tbody>
</table>

- All patients were 60 or younger
- Myeloablative conditioning
- Matched related donors only
- Prior to HMA era

Cutler CS et al, Blood 2004;104:579-585

### Azacitidine Before Transplant

- Retrospective study of 265 patients who underwent alloSCT

<table>
<thead>
<tr>
<th>3 yr outcomes</th>
<th>OS</th>
<th>EFS</th>
<th>Relapse</th>
<th>NRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA</td>
<td>55%</td>
<td>42%</td>
<td>40%</td>
<td>19%</td>
</tr>
<tr>
<td>ICT</td>
<td>48%</td>
<td>44%</td>
<td>37%</td>
<td>20%</td>
</tr>
<tr>
<td>AZA-ICT</td>
<td>32%</td>
<td>29%</td>
<td>36%</td>
<td>35%</td>
</tr>
</tbody>
</table>

- No statistically significant differences

Damaj G et al, JCO 2013:4533-4540

### Our Patient

- Was enrolled on a clinical trial with IV rigosertib, and achieved a bone marrow remission with hematologic improvement
- She recently received allogeneic stem cell transplantation from an unrelated donor.
Summary/Conclusions

- MDS is a complex and heterogeneous group of bone marrow malignancies
- Accurate diagnosis and risk stratification of MDS are essential in determining goals of care and appropriate management
- Lower-risk disease: observation, growth factors, lenalidomide, and immunosuppressive therapy
- Higher-risk disease: hypomethylating agents, possible allogeneic stem cell transplantation
- AlloSCT offers a chance at cure, but is also associated with significant toxicity