What is MDS?

• MDS is the name of a group of conditions that occur when the blood forming cells in the bone marrow are damaged.

• This damage leads to low numbers of one or more type of blood cells:
  – Low WBC: neutropenia (causes infection)
  – Low RBC: anemia (causes fatigue, SOB)
  – Low platelets: thrombocytopenia (causes bruises/bleeds)
Normal Bone Marrow

- Bone marrow is where the cells that make our blood forming cells live
- A small fraction of the blood forming cells are called Stem cells
- A Stem cell will divide and make 2 cells, one that stays a stem cell and another that makes a blood cell
- There are 3 blood cells: WBC, RBC, platelets

Normal Pathway

Myelo-dysplastic Syndrome

- Myelo = marrow (greek)
- Dysplastic = abnormal appearance of cells
  - Funny-looking
  - Differences in shapes, sizes, granules
  - Can be caused by many medical conditions, not only MDS
- Syndrome = collection of signs and symptoms associated together
**MDS: Signs and Symptoms**

- **Neutropenia**
  - Active infection (sinusitis, bronchitis, pneumonia)
  - Risk of infections
- **Anemia**
  - Fatigue, pallor (pale)
  - Short of breath, decreased exercise tolerance
  - Exacerbation of heart failure, angina (chest pain)
- **Thrombocytopenia**
  - Petechiae, bruising, bleeding
  - Risk of bleeding

**MDS: Medical Definition**

- Heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, progressive pancytopenia, morphologic abnormalities and propensity to transform to AML
- **Dysplastic hematopoiesis**
  - Impaired differentiation
  - Accumulation of blasts
  - Hypercellular bone marrow in 90%
- **Peripheral cytopenias**
- **Abnormal bone marrow cytogenetics**

**Myelodysplastic Syndromes**

- 15,000 - 25,000 new cases/year
- Median age > 60 (70% > 50 years) M > F
- **Bone Marrow Failure State**
  - Patients present with fatigue or infections or bleeding
  - In high risk MDS there is a risk of transformation to AML
  - Allo BMT only curative option
Age-related Incidence of MDS:


<table>
<thead>
<tr>
<th>Age (in 5-year blocks)</th>
<th>Incidence rates (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 50</td>
<td>0.5</td>
</tr>
<tr>
<td>50-59</td>
<td>5.3</td>
</tr>
<tr>
<td>60-69</td>
<td>15</td>
</tr>
<tr>
<td>70-79</td>
<td>49</td>
</tr>
<tr>
<td>80 and over</td>
<td>15</td>
</tr>
</tbody>
</table>

Risk Factors: “Why did I get MDS?”

- Cause is unknown in >80% patients
- Prior exposure to chemotherapy and/or radiation
- Advancing age
- Congenital disease (Fanconi anemia, congenital neutropenia, rare familial MDS)
- Environmental toxins (organic solvents, benzene, Hiroshima)

Predisposition to MDS

Heritable:
- Constitutional genetic disorders
- Trisomy 8 mosaicism
- Familial monosomy 7
- Neurofibromatosis 1
- Embryonal dysgenesis (del 12p)
- Congenital Neutropenia
- X-linked sideroblastic anemia, Schimke's ataxia
- DNA repair deficiencies
- Fanconi anemia, AT, Bloom syndrome
- Pharmacogenomic polymorphisms (GSTq1-null)

Acquired:
- Senescence
- Mutagen/Genotoxic Stress
- Pharmacogenomic polymorphisms
- Topoisomerase II agents
- Alkylating agents
- Environmental/occupational
- Aplastic anemia
- PNH

How Does MDS Happen?

Stem Cell gets damaged

DNA Damage
- Genetic
- Mutations
- Environmental

Epigenetics

Bone Marrow Failure: Other Causes

- Nutritional (vitamin B12, folate, iron)
- Toxins (alcohol, medications)
- Chronic disease, viral infections

- Aplastic anemia (AA)
- Pure red blood cell aplasia
- Paroxysmal nocturnal hemoglobinuria (PNH)

- Systemic mastocytosis
- Hairy Cell Leukemia (HCL)
- Large granular lymphocyte disease (LGL)
- Other malignancies

Clinical Overlap / Associations:

- Acute Myeloid Leukemia
- Myeloproliferative Disease
- Paroxysmal Nocturnal Hemoglobinuria
- Hypocellular MDS
- Autoimmune diseases
  - Aplastic Anemia
  - LGL leukemia
  - Pure Red Cell Aplasia
MDS: Diagnostic Evaluation

- Peripheral blood count (CBC with differential and smear)
- Bone marrow biopsy and aspiration
  - Bone marrow blasts%
  - Cytogenetics
  - Iron stain
  - Reticulin stain
- Additional tests
  - Iron saturation, ferritin/TIBC
  - B12, folate levels
  - EPO level

Establish diagnosis of MDS & determine subtype & prognosis:
- FAB/WHO Classification
- IPSS score

How Do We Classify MDS?

<table>
<thead>
<tr>
<th></th>
<th>IPSS 1997</th>
<th>WPSS 2007</th>
</tr>
</thead>
</table>

FAB vs WHO Classification

<table>
<thead>
<tr>
<th>FAB</th>
<th>WHO</th>
<th>Dysplasia(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>5q-Syndrome</td>
<td>Erythropoietic</td>
</tr>
<tr>
<td>RA</td>
<td>RA</td>
<td>Erythropoietic</td>
</tr>
<tr>
<td>RCMD</td>
<td>2-3 lineages</td>
<td></td>
</tr>
<tr>
<td>MDS-U</td>
<td>1 lineage</td>
<td></td>
</tr>
<tr>
<td>RARS</td>
<td>RARS</td>
<td>Erythropoietic</td>
</tr>
<tr>
<td>RAEB</td>
<td>RAEB-1</td>
<td>1-3 lineages</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>AML</td>
<td></td>
</tr>
<tr>
<td>CMML</td>
<td>CMML (if WBC &lt; 13,000/uL)</td>
<td></td>
</tr>
</tbody>
</table>
IPSS Scoring System
(800 de novo MDS patients)

• Overall prognostic score based on:
  1. Number of cell lines that are low (1, 2 or 3)
  2. Bone marrow blasts (%)
  3. Cytogenetics (karyotype)

• Stratifies patients into 4 risk groups
  – Predict survival
  – Predict time to AML transformation


IPSS Scoring System & Risk:

<table>
<thead>
<tr>
<th>Prognostic Variables</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Marrow Blasts</td>
<td>&lt;5</td>
<td>5-10</td>
<td>11-20</td>
<td>21-30</td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good</td>
<td>Int</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenia</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Risk</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Int 1</td>
<td>0.5-1.0</td>
<td></td>
</tr>
<tr>
<td>Int 2</td>
<td>1.5-2.0</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>≥ 2.5</td>
<td></td>
</tr>
</tbody>
</table>

High risk


Survival and AML Progression
IPSS MDS Risk Classification

Higher risk MDS (INT-2, High) is associated with a median survival of 0.4—1.2 years

### Outcomes For Patients With MDS

<table>
<thead>
<tr>
<th>IPSS Score</th>
<th>Risk Group</th>
<th>Median Survival (yrs)</th>
<th>25% progression to AML (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Low</td>
<td>5.7</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>0.5-1 Int-1</td>
<td>3.5</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>1.5-2 Int-2</td>
<td>1.2</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>&gt;2 High</td>
<td>0.4</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

These outcomes are based on UNTREATED patients


---

### Revised IPSS

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>very good</td>
</tr>
<tr>
<td>BM blast, %</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Platelets, x 10^9/L</td>
<td>&gt;100</td>
</tr>
<tr>
<td>ANC x 10^9/L</td>
<td>&gt;0.8</td>
</tr>
</tbody>
</table>


---

### Revised IPSS Risk Score

<table>
<thead>
<tr>
<th>Risk</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>&lt;1.5</td>
</tr>
<tr>
<td>Low</td>
<td>1.5 to 3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3.0 to 4.5</td>
</tr>
<tr>
<td>High</td>
<td>&gt;4.5 to 6.0</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;6</td>
</tr>
</tbody>
</table>

IPSS-R Survival Related to Age

<table>
<thead>
<tr>
<th>No. pts</th>
<th>Very Low</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients 7012</td>
<td>19%</td>
<td>38%</td>
<td>20%</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Survival, All (Years)</td>
<td>8.8</td>
<td>5.3</td>
<td>3.0</td>
<td>1.6</td>
<td>0.76</td>
</tr>
<tr>
<td>Hazard ratio [95% CI]</td>
<td>0.5 [0.46-0.59]</td>
<td>1.0 [0.93-1.1]</td>
<td>2.0 [1.8-2.1]</td>
<td>3.2 [2.9-3.5]</td>
<td>8.0 [7.2-8.8]</td>
</tr>
</tbody>
</table>

| Patients 6485 | 19% | 37% | 20% | 13% | 11% |
| AML/25% (Years) | NR [14.5-NR] | 10.8 [9.2-NR] | 3.2 | 1.4 | 0.73 |
| Hazard ratio [95% CI] | 0.5 [0.4-.6] | 1.0 [0.86-1.2] | 3.0 [2.7-3.5] | 6.2 [5.4-7.2] | 12.7 [10.8-15.2] |


WPSS

- Uses WHO based morphology
- Bone marrow chromosome changes
- P-RBC transfusion requirements

MDS Simplified (low vs high)

- **Low Risk**
  - RA, RARS
  - RCMD, RCMD-RS
  - MDS-U, MDS del (5q)
  - IPSS Low, Int-1 (score 0-1), IPSS-R Vlow, Low

- **High Risk**
  - RAEB (1 or 2)
  - IPSS Int-2 and high (score >/= 1.5); IPSS-R High, V High
Why Classify?

• Not meant to scare you
• Scores used to help direct WHEN to treat and when NOT to treat
• Helps to direct WHAT therapy to start
  – Low risk
  – High risk

Treatment GOALS in MDS

<table>
<thead>
<tr>
<th>Low IPSS</th>
<th>INT-1 IPSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve marrow function</td>
<td></td>
</tr>
<tr>
<td>Decrease Transfusion Needs</td>
<td></td>
</tr>
<tr>
<td>Decrease impact of MDS on QOL</td>
<td></td>
</tr>
<tr>
<td>Establish careful monitoring plan</td>
<td></td>
</tr>
<tr>
<td>Stabilize marrow function</td>
<td></td>
</tr>
<tr>
<td>Lower risk transformation</td>
<td></td>
</tr>
<tr>
<td>Move to definitive therapy OK</td>
<td></td>
</tr>
<tr>
<td>Trilineage marrow improvement</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Options For LR-MDS

• Observation/Wait and Watch
• Supportive transfusions (RBC and platelets)
• Iron overload/chelation
• Hematopoietic Growth Factors (Synthetic versions of proteins normally made in the body to stimulate growth of red cells, white cells and platelets)
• Immunosuppressive therapy (ATG, cyclosporine)
• Immunomodulatory drugs (Lenalidomide)
Supportive Care

- Anti-microbial care if neutropenic
  - Acyclovir, fluconazole
  - Neutropenic precautions (sushi, raw oysters)
- Red Blood Cell Transfusions
  - 2 units/mo (moderate)
  - 4 units/mo (high) (100 units over 2 years)
  - 100 units ~≈~ 20 grams iron
- Iron chelation
  - Deferoxamine can improve survival and decrease liver/endocrine complications (kids/thalassemia)

Iron Overload

- Serum ferritin concentration (>1000 microg/L)
- Evidence of organ related damage (liver, heart)
- Liver biopsy
  - Standard for kids, not feasible in MDS pts
- MRI
  - Investigational, potential for broad access
- Magnetic susceptometry (SQUID)
  - Investigational, very limited access

Prospective Chelation Study in Lower-Risk MDS: 48 Month Update-OS

- 5 yr noninterventional registry study, N=599 pts from 107 US Centers
- Lower-risk MDS and transfusional iron overload tx +/- chelation
  At 48 mo, chelation pts had longer OS vs non-chelated (>4 yrs)

Prospective Chelation Study in Lower-Risk MDS: 48 Mo Update-AML Transformation

- At 48 months, chelated pts had significantly longer time to AML transformation versus no chelation (>2 yrs)
  - Non-chelated (n=330) = 45.6 mo
  - Chelated (n=269) = 67.6 mo
  - Chelated > 6mo (n=202) = 77.0 mo
- Percentages of pts who progressed to AML similar in both groups (7% vs 10%)


Deferoxamine (Desferal)

- Challenges of therapy
- Subcutaneous or IV administration
- Continuous 12 hour infusion 5-7 days/ wk
- Infusion site reactions and pain
- Eye and ear side effects, need periodic exams
- Infectious complications (fungal)
- Oral version (EXJADE)....nausea and $$$

Growth Factors

- Granulocyte Colony Stimulating Factor (GCSF, Neupogen ®)
- Granulocyte –macrophage Colony Stimulating Factor (GM-CSF, Leukine ®)
- Peg-filgrastim (Neulasta ®)
- Erythropoietin (EPO, Procrit ®, Epogen ®)
- Darbepoietin (Aranesp ®)
- Thrombopoietin (TPO, romiplostim, Nplate ®)
- Note, these are not FDA approved for MDS
Erythropoietin Stimulating Agents (ESAs) in MDS

- Anemia is present in >80% of MDS pts
- Transfusions help but many issues
  - Iron overload, fluid overload, antibody production
- Recombinant EPO is FDA approved for treating anemia associated with kidney failure
- Has been used since about 1990 in MDS
- Response rates in about 15-30% of patients
- Many studies done in >1000 pts
- Part of the NCCN MDS treatment guidelines

Erythropoietin (ESAs) in MDS

- Often high endogenous epo levels
- Many different doses and schedules
- Higher response rates with epo + G-CSF if epo <500mU/mL and transfusions <2U/month
- Poor probability of response if epo >500mU/mL and transfusions >2U/month


MDS: Patient Selection For ESAs

- Good response (74%, n=34)
- Intermediate response (23%, n=31)
- Poor response (7%, n=26)

Treatment response score:
- RA, RARS, RAEB
- Score > +1
- Score = -1
- Score < -1
- s-epo <100 U/L +2
- 100-500 U/L +1
- >500 U/L -3
- Transf <2 units/m +2
- >=2 units/m -2
- U RBC/m = or >3 units/m +2
- <3 units/m -2

**ESAs in MDS**
- Varying response criteria in clinical trials ~40%
- Usually complete response is an increase in HgB to at least 11.5 without transfusions, partial response is an increase of HgB by at least 1.5 g/dl or reduction in transfusion requirements
- Responses usually in 12-16 weeks
- Generally well tolerated
- **Side effects:** hypertension, fever, headache, nausea, chest pain

**ESA’s: Side Effect Issue**
- Studies of EPO in solid tumor patients showed increased heart attacks, stroke, heart failure, blood clots, increased tumor growth, death, especially when HgB >12
- Has resulted in concern for MDS patients but NO DATA yet showing these effects in MDS pts.
- Has had major effects on insurance coverage

**ESAs**
- EPO and G-CSF treatment associated with improved survival in MDS
- Mostly low risk patients
- Erythroid response 39% med duration 23 months
- Improved survival in pts requiring fewer than 2u per month
- No increase in AML

Jadersten et al, JCO, vol 26, July 2008
**ESA’s: Summary**

- Not likely able to get this therapy unless HgB <10 (insurance company will deny coverage)
- Don’t stay on it if it is not working (Stop after 12-16 weeks if not improved)
- Can alter your bone marrow biopsy results
- In patients with RARS, use it in combination with G-CSF

**Stimulating WBC With G**

- Not routine
- Active infections, recurrent/resistant infections, neutropenic fever
- Can be combined with ESA’s to improve responses in some patients (i.e. RARS)
- Side effects: fever, bone pain, injection site reactions
- Does stimulating white cells cause leukemia?

**Romiplostim**

- In patients receiving 5AC, Romiplostim vs placebo
  - Increased PLT count over time and increases PLT count nadir during tx cycles
  - Reduced incidence of clinically significant thromocytopenic events (bleeds)
  - Reduced incidence of PLT transfusions
- Romiplostim plus 5AC well tolerated

Giagounidis, A. et al, Tx with Romiplostim in thrombocytopenic pts with Low or Int-1 Risk MDS: Results of a Randomized DB Placebo Study. ASH 2011
Lenalidomide in MDS With Del 5q

• Improvement in MDS
  – Duration of transfusion independence (>2.2 years)
  – HgB increased (median 3.2 g/dL)
  – Time to initial response (4.5 wk)

• Practical issues with Lenalidomide
  – CBC weekly for at least first 8 weeks, significant neutropenia and thrombocytopenia
  – Dose adjustments needed

Epigenetic Therapies

• Azacitidine (Vidaza)
• Decitabine (Dacogen)

Epigenetics

• Inheritable changes in gene expression patterns that are not due to DNA sequence
• Changes mediated by covalent attachment of chemical groups (i.e. acetyl, methyl) to DNA and associated proteins (chromatin, histones)
• Key in modifying differential expression of genes and defining cellular identity
• Key in transforming normal to malignant cells
Promoter Methylation in Cancer

Genetic + epigenetic changes that inactivate tumor suppressor genes: Knudson two-hit hypothesis

Herman and Baylin NEJM 2003
What to Expect: Azacitidine/Decitabine

- Given every 28 days (once a month)
  - AZA 75mg/m² SC or IV x 7 days every month
  - DAC 20mg/m² IV x 5 days every month
- Need to give at least 4-6 cycles
  - Side effects: nausea, vomiting, decreased counts (WBC, RBC, platelets), fatigue, fevers, infections
  - Side effects are manageable: antibiotics, anti-emetics and transfusions

Questions??
Treatment GOALS in MDS

- **Low IPSS INT-1 IPSS**
  - Improve marrow function
  - Decrease Transfusion Needs
  - Decrease impact of MDS on QOL
  - Establish careful monitoring plan

- **INT-2 IPSS High IPSS**
  - Stabilize marrow function
  - Lower risk transformation
  - Move to definitive therapy
  - Trilineage marrow improvement

Treatment Options for LR-MDS

- Observation/Wait and Watch
- Supportive transfusions (RBC and platelets)
- Iron overload/chelation
- Hematopoietic Growth Factors (Synthetic versions of proteins normally made in the body to stimulate growth of red cells, white cells and platelets)
- Immunosuppressive therapy (ATG, cyclosporine)
- Immunomodulatory drugs (Lenalidomide)

Treatment Options for HR-MDS

- Azacitidine (Vidaza) or Decitabine (Dacogen)
- Lenalidomide (Revlimid)
- Intensive chemotherapy
- Bone Marrow Transplant
- Clinical Trials
CALGB #9221 Trial Design
A Randomized Phase III Controlled Trial of Subcutaneous Azacitidine in Myelodysplastic Syndromes

RA
RARS
RAEB
RAEB-T
CMML

1) Observation
Exit
Continue until
Endpoint
Yes
No
Aza C (dose as per arm #2)

2) Aza C 75 mg/m²/d x 7 days q28 x 4

QOL
M M M
0 15 20
Day
65 113

QOL
M M M

* Minimum duration of observation = 4 months
QOL = Quality-of-life assessment
M = Bone marrow
Aza C = azacitidine S.C.

Analysis of Response

SC
AZA
Crossover

No. Evaluated
92
99
49

CR
0 (0%)
7 (7%)*
5 (10%)

PR
0 (0%)
15 (16%)**
2 (4%)

Improved
5 (5%)
38 (37%)**
16 (36%)

Total
5 (5%)
60 (60%)**
23 (47%)

P - value
* < 0.01
**<0.001

Time to AML Transformation

Probability of Remaining Event-Free

Azacitidine
Supportive Care

p=0.001
p=0.007

Silverman L, et al. JCO 2002
Azacitidine and QoL

• Improvement in
  – Fatigue
  – Dyspnea
  – Physical functioning
  – Positive affect
  – Psychologic distress
• 45% became transfusion independent
• 9% had a 50% reduction in transfusions

Most Common Side Effects

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Observation (N=92)</th>
<th>All Azacitidine (N=220)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>16 (17.4%)</td>
<td>155 (70.5%)</td>
</tr>
<tr>
<td>Anemia NOS</td>
<td>59 (44.1%)</td>
<td>152 (69.5%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>42 (45.7%)</td>
<td>144 (69.5%)</td>
</tr>
<tr>
<td>Vomiting NOS</td>
<td>5 (5.4%)</td>
<td>119 (54.1%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28 (30.4%)</td>
<td>114 (51.8%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>27 (29.3%)</td>
<td>106 (48.2%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>13 (14.1%)</td>
<td>80 (36.4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (14.1%)</td>
<td>80 (36.4%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10 (10.9%)</td>
<td>71 (32.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (25.0%)</td>
<td>79 (35.9%)</td>
</tr>
<tr>
<td>Injection Site Erythema</td>
<td>0 (0.0%)</td>
<td>77 (35.0%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (6.5%)</td>
<td>74 (33.6%)</td>
</tr>
<tr>
<td>Necropenia</td>
<td>10 (10.9%)</td>
<td>71 (32.3%)</td>
</tr>
<tr>
<td>Erythromas</td>
<td>14 (15.2%)</td>
<td>67 (30.5%)</td>
</tr>
</tbody>
</table>

Azacitidine Survival Study (AZA-001)

BSC was included with each arm. Tx continued until unacceptable toxicity, AML transformation, or disease progression.

Overall Survival: Azacitidine vs CCR

- Log-Rank p=0.001
- HR = 0.58 [95% CI: 0.43, 0.77]
- Deaths: AZA = 82, CCR = 113
- Difference: 9.4 months

Decitabine (DAC) Phase III MDS Trial Study Design

- Decitabine + Supportive Care
  - 15mg/m² over 3 hours q8h x 3 days q6wks (N=89)
- Supportive Care
  - ABX, GFs and/or Transfusions (N=81)

Stratification
- IPSS
- Type of MDS (primary or secondary)

Eligible Patients (n=170)

Response assessed after 2nd cycle, with 2 more cycles given if CR

Decitabine Phase III MDS Trial
Most Common Grade 3/4 Adverse Events (≥10%)

Of the 83 DAC treated pts, 8 stopped therapy for adverse events

<table>
<thead>
<tr>
<th></th>
<th>Decitabine (n=83)*</th>
<th>Supportive Care (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10%</td>
<td>77%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22%</td>
<td>63%</td>
</tr>
<tr>
<td>Anemia</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>17%</td>
<td>6%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>8%</td>
<td>14%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>13%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Those patients exposed to decitabine

DAC Phase III: Time to AML or Death

Why Does DAC Not Show Survival Benefit?

- Number of cycles given was less
- Different populations of patients
  - Duration of MDS
  - Cytogenetic risk
  - Performance status
  - Transfusion requirements
- Drug delivery different (shorter time)
  - 15mg/m² IV Q8 x 3days
  - 20mg/m² IV QD x 5 days

*Steensma, et al, JCO 2009
General HMA Recommendations

• EARLY declaration of failure may be a mistake as responses can be seen after cycle 6
• Continuous dosing is recommended as long as pts are responding/stable (i.e., DON'T STOP!)
• Drug holidays are NOT recommended as pts who progress are less likely to respond when re-challenged with drug
• Dose reductions are favored for pts on long-term treatment who develop cytopenias (vs. prolonged dosing intervals)
• Bone marrow evaluation suggested for every 4-6 cycles in responding pts

Therapy for HR-MDS

• Azacitidine or Decitabine
  – Clinical responses 35-50%
  – Improves QoL (i.e. decreased transfusions)
  – Decrease risk of progression to AML
  – Improve survival (AZA only)
  – Need 4 to 6 cycles of therapy to assess response
  – If respond, then continue as long as side effects tolerable
  – Not a cure

• Bone Marrow Transplant
  – cure

BMT: How To Decide

• Is the patient strong/fit enough for BMT?
• Is there a donor?
• Risks: infection risk, organ damage and graft versus host disease (new immune system attacks patient normal cells not just the MDS), death from procedure (15-30%).
• Need to balance the risk of disease progression to risk of treatment.
### Stem Cell Transplant: Approximate Life Expectancy (yrs)

<table>
<thead>
<tr>
<th></th>
<th>Immediate BMT</th>
<th>Transplant in 2 yrs</th>
<th>Transplant at progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>6.51</td>
<td>6.86</td>
<td>7.21</td>
</tr>
<tr>
<td>Int-1</td>
<td>4.61</td>
<td>4.74</td>
<td>5.16</td>
</tr>
<tr>
<td>Int-2</td>
<td>4.93</td>
<td>3.21</td>
<td>2.84</td>
</tr>
<tr>
<td>High</td>
<td>3.20</td>
<td>2.75</td>
<td>2.75</td>
</tr>
</tbody>
</table>


### RIC vs High Dose Conditioning BMT

Scott et al., Leukemia 2008

### BMT: What To Expect

- Standard full ablation for pts <65 years old
- Check for a full match from siblings or national registry (blood test takes about 2-4 weeks for results)
- Full BMT: Inpatient stay 3-6 weeks for chemotherapy, transplant infusion, and monitor counts (transfusion dependent) and manage infections
- Alternative transplants from half match /cord
  - can use siblings, parents, children in pts >65 y.old
Conclusion: High Risk MDS

- Hypomethylating agents
  - AZA
  - DAC

- Bone marrow transplant
  - Full myeloablative
  - Non-myeloablative

- Clinical trials

New Treatments for MDS: What’s on the Horizon?

Hetty Carraway, MD, MBA
Taussig Cancer Institute
Cleveland Clinic
July 26, 2014

Outline

1. Biology (via mutation annotation)
2. Treatment MDS
3. Novel Agents in MDS
Clonal Evolution MDS to sAML

Walter MJ et al. NEJM 2012;366:1090-1098

TP53 Mutations Are Present in The HSC Prior To Chemotherapy

- Whole genome sequencing from t-AML at time of diagnosis shows TP53 mutational burden similar in t-AML/t-MDS and de novo MDS/AML.
- HSCs with TP53 mutations present prior to chemotherapy due to normal aging (as low as 0.1% frequency)


Landscape of Genetic Aberrations in MDS

- 944 pts with various MDS subtypes
- Screened for mutations and deletions in 104 known MDS-related genes
- Only 6 genes were mutated in >10% cases:
  - TET2, SF3B1, ASXL1, SRSF2, DNMT3A, and RUNX1
- Intratumoral genetic heterogeneity noted in 48.3%

Molecular Genetics

• ASXL1, EZH2, ETV6, RUNX1, TP53

• Prospective studies still needed to evaluate for signature responsive mutation patterns to therapies.

• Targeted therapies to specific mutations are also in development (IDH1/IDH2/SF3B1)

Genoptix: (MDS Molecular Profile: the above 5 genes) (Myeloid Molecular Panel by NextGen Sequencing with 21 genes panel SF3B1, SETBP1, TET2, IDH1, IDH2, CBL, NRAS, KIT, JAK2, MPL, NPM1)

Prognosis: Landscape of Genetic Aberrations in MDS

• The mutation/deletion status of a set of 14 genes can be used as variables independent of clinical parameters to construct a prognostic score
  – Cox regression (proportional hazards model) based on 14 genes plus age, sex, WBC, Hb, platelets, IPSS-R cytogenetic score

• Novel prognostic molecular model showed significant 3 year OS differences by risk group
  – Low risk: 95% survival at 3 yrs (p<0.001)
  – Intermediate risk: 69%
  – High risk: 32%
  – Very high risk: 5%


5AC Treatment for Pts with MDS and/or AML Harboring Chromosome 3q Abnormalities

• Chr 3 abnormalities (including aberrant expression of EVI-1) represent a small subset of patients

• Chr 3 abnormal MDS or AML is associated with poor outcomes using conventional chemotherapy, <10% 3 yr survival

• In this retrospective study, MDS or AML pts with Chr 3 abnormality (N=184) had improved OS to 5AC than pts not harboring Chr 3 abnormality (N=400) (13 mo OS versus 8 mo, p=0.02)

• Median OS=10.5 mo.
• Noted 3q21 had 74 mo survival

• 5AC should be considered as upfront therapy for Chr 3 MDS or AML rather than CCR; including pts eligible for BMT.

Can We Improve Epigenetic Therapy?

- **Dose and Duration Single Agent**
- **Combination**
  - Other epigenetic agents (HDAC i, chromatin modifiers)
  - Chemotherapy (immunomodulatory compounds)
    - Lenalidomide
    - Vorinostat
- **Maintenance HMA**
  - Post chemotherapy and pre/post BMT
- **Drug design/Select target patient(s)**
  - Gene methylation profile, TET2 mutation status, miR-29b exprsn


**5AC vs 5AC + Entinostat For Myeloid Neoplasms: E1905**

<table>
<thead>
<tr>
<th></th>
<th>Arm A 5AC 50mg/m2 x 10d (%)</th>
<th>Arm B 5AC 50mg/m2 x 10d + Entinostat D0 and D10 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>Tri-lineage response= 31%</td>
<td>Tri-lineage response= 24%</td>
</tr>
<tr>
<td>Partial remission</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>Trilineage HI</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>HI not trilineage</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>No response</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>CR/PR/THI</td>
<td>31</td>
<td>24</td>
</tr>
</tbody>
</table>


**5AC vs 5AC + Entinostat For Therapy Related Myeloid Neoplasm: E1905**

- 47 pts with t-MN (29 MDS/18 AML) in E1905
- 5AC may be best approach (over chemo) given track record in other poor risk clinical presentations (del7)
- 5AC monotherapy x10d appears effective

<table>
<thead>
<tr>
<th></th>
<th>Arm A 5AC alone</th>
<th>Arm B 5AC + MS-275</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of t-MN pts</td>
<td>24</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>CR/PR/THI (%)</td>
<td>11/24 (46%)</td>
<td>4/23 (17%)</td>
<td>p=0.06</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>12.8</td>
<td>5.7</td>
<td>p=0.008</td>
</tr>
</tbody>
</table>

Experience With Combination Epigenetic Agents in MDS/AML

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Agents</th>
<th>CR (%)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gore</td>
<td>36</td>
<td>5AC/PB</td>
<td>14</td>
<td>38</td>
</tr>
<tr>
<td>Gore</td>
<td>27</td>
<td>5AC/MS275</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>Somerso</td>
<td>53</td>
<td>5AC/VPARA/RA</td>
<td>22</td>
<td>42</td>
</tr>
<tr>
<td>Garcia-Manero</td>
<td>37</td>
<td>5AC/MGD0103</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Silverman</td>
<td>24</td>
<td>5AC/Vorinostat</td>
<td>45</td>
<td>52</td>
</tr>
<tr>
<td>Garcia-Manero</td>
<td>54</td>
<td>DAC/VPA</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Blum</td>
<td>28</td>
<td>DAC/VPA</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>Issa</td>
<td>32</td>
<td>DAC/Vorinostat</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Yee</td>
<td>27</td>
<td>DAC/Vorinostat</td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
</table>

A Phase II Trial of Epigenetic Modulators Vorinostat in Combination with 5AC in Pts with MDS: Initial Results

- Combination is safe
- Deliver multiple cycles
- Suggestive that combination therapy is better than monotherapy
- Cohort 2 +3 associated with longer duration of response (V for 7d)
- Intergroup Study SWOG 1117 ongoing (uses cohort 2)

North American Intergroup Randomized Phase 2 MDS Study: S1117

- Higher-risk MDS (IPSS >1.5)
- AZA N=80
- AZA + LEN N=80
- AZA + VORIN N=80
- Groups: SWOG, ECOG, CALGB, NCIC
- Total Sample Size: 240
- Primary Objective: 20% improvement of RR based on 2006 IWG Criteria
- Secondary Objectives: OS, RFS, LFS
- Power 81%, alpha 0.05 for each combo arm vs. AZA
- Anticipated time: 2.5 years


Combination Therapy with Mocetinostat, An Oral, Spectrum-Selective HDAC Inhibitor, and SAC

- Phase 1/2 study, 66 pts w/ MDS and AML
- Mocetinostat, spectrum selective, non-hydroxamate HDACi targeting HDACs 1,2,3,11
- Phase 1: N=24, dose levels 35-135mg 3x/wk start D5
- Phase 2: N=42, doses 90 or 100mg
- Sub-set analysis of only MDS pts, N=22 (blasts 5-20%)
  - Median age 73 yrs
  - 59% (13/22) CR and CRi
  - 9 prev treatments, 13 no prior treatments
  - 35% (6/22) gained transfusion independence (RBC/PLT)
- Active plan to move this combination to randomized Phase 2


Phase II Study: Novel SQ Hypomethylating Agent SGI-110 in Adults With AML

- SGI-110: dinucleotide of decitabine and deoxyguanosine
- Increases in vivo exposure of decitabine by blocking deamination

- Elderly AML
  - RR_AML or tx-naive pts ≥ 65 yrs of age
  - Not fit intensive Tx
  - ECOG PS 2 (N = 90)

- Primary endpoint: ORR (CR/CRp/CRi)
- Secondary endpoints: safety, DOR, OS


Novel SQ Hypomethylating Agent SGI-110 in Adults With AML

- N=90 pts RR/AML in Phase 2
- 43% remission rate in tx-naive patients with AML ≥ 65 yrs of age
- 16% remission rate in relapsed/refractory AML
- Comparable remission rates at 60 mg/m² and 90 mg/m²

Novel SQ Hypomethylating Agent SGI-110 in Adults With AML: Adverse Events


<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades</th>
<th>Grades 3/4</th>
<th>All Grades</th>
<th>Grades 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site pain</td>
<td>35</td>
<td>0</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>30</td>
<td>26</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Anemia</td>
<td>21</td>
<td>14</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>0</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>12</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>5</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Injection-site hemorrhage</td>
<td>12</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>12</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>2</td>
<td>23</td>
<td>0</td>
</tr>
</tbody>
</table>

30-day mortality
- 60 mg/m²: n = 4 (7.0%)
- 90 mg/m²: n = 7 (12.3%)

60-day mortality
- 60 mg/m²: n = 7 (16.3%)
- 90 mg/m²: n = 9 (20.0%)

Overall Survival in High Risk MDS After Azacitidine Failure


Median OS=17 mo; TFS=15 mo

Overall Survival in Low and Int-1 Risk MDS After HMT Failure

Median OS=17 mo; TFS=15 mo

**Limited Options for MDS Pts Failing HMT**

- Alternate HMA (5AC vs DAC vs novel formulation)
- Induction Chemotherapy (Standard +/- Novel agent)
- Clinical Trial (Rigosertib)
  - PLK-1 pathway inhibitor and PI3 kinase inhibitor
  - Did not show improved overall survival compared to best supportive care in Phase 3 "ONTIME Trial"
- Clinical Trial (PD-1 inhibition +/- 5AC or DAC)
  - PD-1 pathway plays critical role in tumor immune evasion
  - PD-1 receptor-ligand interaction: major pathway hijacked by tumors to suppress immune control

Greenberg ASH 2011 and Konrokji 2013

**The Targeted HDACi Tenfinostat Shows Selective In Vitro Efficacy in Monocytoid Lineage AML**

- Tenfinostat (CHR-2845): novel monocyte/macrophage targeted HDACi that is cleaved by hCE-1 (into CHR-2847)
- hCE-1 (human carboxylesterase-1) is an intracellular esterase found only in cells of monocytoid lineage and hepatocytes
- Novel agent can decrease the known side effect profile of HDACi
- Accumulation of CHR-2847 in hCE expressing cells results in 20-100 fold increase in potency
- *in vitro* efficacy of T tested in primary AMLs from 70 pt samples
- Dose dependent induction of apoptosis and growth inhibitory effects seen with T in M4/M5 AML samples
- No growth inhibitory effects seen on normal bone marrow cells (n=5)

Zakrzewicz J, et al. ASH 2013. Abstract 1297

**Evaluation of CD33 Expression and Functional Analysis of the CD33/CD3 Bispecific BITE Antibody AMG 330 in Primary AML Samples**

- AMG-330 is a bispecific T cell engager (BiTE)
- CD33 is expressed on up to 90% leukemia cells
- T cell activation and tumor cell lysis occurred when leukemia blasts were exposed to AMG 330 *in vitro* (even if they harbored low levels of CD33)
- Clinical trial is planned using AMG330 in patients with low risk MDS in 2014-2015

Clinical Trials: Alternative BMT

• Age less than 65
  – Myeloablative Transplants

• Reduced Intensity Transplant (Age less than 75)
  – Non-myeloablative
• Haploidentical Transplant
• Cord Blood Transplants

Allogeneic BMT

**Ufront**
• Encouraged if suitable donor available and pt age is <65 years¹
• May obtain better outcome if in CR/PR/HR from HMA therapy prior to BMT²
• Cure ~ 40% pts

**Relapsed Setting**
• Clinical trials ongoing
• Low intensity Clofarabine as bridge to RIC-BMT³
  – N=29 pts
  – OS=71%, OS@2 yr=30%
  – Clo start day minus 20
• High intensity chemo to BMT

5AC Salvage post-Allo BMT

<table>
<thead>
<tr>
<th>Setting</th>
<th>Study Type</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC</td>
<td>Post-salvage</td>
<td>45</td>
<td>40% DFS</td>
</tr>
<tr>
<td>SKCCG</td>
<td>Relapse post</td>
<td>10</td>
<td>6 CR</td>
</tr>
<tr>
<td>German Cooperative SCT</td>
<td>Relapse post</td>
<td>22</td>
<td>5 CR, 4 PR</td>
</tr>
<tr>
<td>Freiburg</td>
<td>Relapse post</td>
<td>28</td>
<td>4 CR</td>
</tr>
</tbody>
</table>

All = ~20% Salvage Rate

Conclusions: MDS

• Mutational analyses are helping to understand biology of MDS and can have valuable applications if tested prospectively.
• Combination epigenetic therapies appear safe/tolerable and seem to have promising responses: awaiting results of randomized studies.
• No new agents exist (yet) that offer improved survival for pts with MDS above results with azacitidine.
• Novel agents are needed
  – watch for results of IDH1/IDH2 inhibitors

Thank you

• Thank you for your questions and for being here today to learn/teach others about MDS.
• Thank you to Cleveland Clinic for allowing me to care for patients with MDS/AML.
• Thank you to my colleagues and the foundations that continue to fight to find better answers for our patients with these diseases.