Myelodysplastic Syndromes
Current Thinking on Disease, Diagnosis and Treatment

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Overview:
Biology and Diagnosis of MDS
Scoring System/Prognosis
Treatment Options for Low Risk MDS
Treatment Options for High Risk MDS

What is MDS?
- 15,000 - 25,000 new cases/year
- Median age 71 M > F
- Clonal disorder: multi-lineage hematopoietic progenitor
- Ineffective hematopoiesis with peripheral cytopenias
- Bone Marrow Failure State:
  - Patients present with fatigue, infection or bleeding
  - Transformation to AML in ~ 1 in 3
  - Allo BMT only curative option


Epidemiology
Overall incidence: 3.4 per 100,000

Incidence Rates, All Races, Both Sexes, 2000-2009


Age-Specific (Crude) SEER Incidence Rates, All Races, Both Sexes, 2000-2009
MDS Pathogenesis

Stage 1: Intrinsic increase in apoptotic response and inflammation
- Enhanced production of pro-inflammatory cytokines
- Impaired hematopoietic microenvironment

Stage 2: Acquisition of anti-apoptotic molecules
- Expression of Bcl-2, Mcl-1
- Suppression of TNFα-induced apoptosis

Stage 3: Initiation of clonal evolution
- Chromosomal abnormalities
- Increased risk of leukemia transformation

Genetic Abnormalities in MDS

<table>
<thead>
<tr>
<th>Translocations/Rearrangements</th>
<th>Uniparental Disomy</th>
<th>Microdeletions</th>
<th>Copy Number Change</th>
<th>Point Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare in MDS</td>
<td>Rare - often seen in point mutations</td>
<td>About 90% of cases</td>
<td>TdT, del(7q)</td>
<td>Most common</td>
</tr>
</tbody>
</table>

Clinical Overlap / Associations:

- Acute Myeloid Leukemia
- Myeloproliferative Disease
- Paroxysmal Nocturnal Hemoglobinuria
- Autoimmune diseases
  - Aplastic Anemia
  - LGL leukemia
  - Pure Red Cell Aplasia

Bone Marrow Failure: Signs and Symptoms

Anemia
- Fatigue, pallor
- Shortness of breath, decreased exercise tolerance
- Exacerbation of heart failure, angina

Neutropenia
- Active infection (bronchitis, sinusitis, pneumonia, etc.)
- Risk of infections

Thrombocytopenia
- Petechiae, bruising, bleeding
- Risk of bleeding

MDS: Diagnostic Evaluation

- Peripheral blood counts + reticulocyte count
- Bone marrow biopsy and aspiration
  - Bone marrow blasts %
  - Cytogenetics
  - Iron stain
  - Reticulin stain
- Additional tests
  - Iron saturation, ferritin
  - B12, folate levels
  - EPO level

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

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


**Performing a bone marrow aspiration**


**Cytologic Dysplasia: Bone Marrow DysErythropoiesis**

Courtesy of Dr. Bennett and Dr. List.

**Cytologic Dysplasia: Marrow and Blood DysGranulopoiesis**

Courtesy of Dr. Bennett and Dr. List.

**Cytologic Dysplasia: Marrow and Blood DysMegakaryopoiesis**

Courtesy of Dr. Bennett and Dr. List.

**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>Sq-Syndrome</td>
<td>Erythopoietic</td>
</tr>
<tr>
<td>RA</td>
<td>RA</td>
<td>Erythopoietic</td>
</tr>
<tr>
<td>MDS-U</td>
<td>RCMD</td>
<td>2-3 lineages</td>
</tr>
<tr>
<td>RARS</td>
<td>MDS-U</td>
<td>1 lineage</td>
</tr>
<tr>
<td>RARS</td>
<td>RARS-RS</td>
<td>2-3 lineages</td>
</tr>
<tr>
<td>RAEB-1</td>
<td>RAEB-1</td>
<td>1-3 lineages</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>RAEB-2</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; 13,000u/l)</td>
<td></td>
</tr>
</tbody>
</table>

How Do We Classify MDS?

**IPSS** 1997

**WPSS** 2007

**FAB** 1970-80

**WHO** 1999

**IPSS-R** 2012


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**IPSS Is Most Common Tool for Risk Stratification of MDS**

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow blasts</td>
<td>≤ 5%</td>
<td>5% to 10%</td>
<td>11% to 20%</td>
<td>21% to 30%</td>
<td>≥ 31%</td>
<td>≥ 41%</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td>2/3</td>
<td>2/3</td>
<td>2/3</td>
<td>2/3</td>
</tr>
</tbody>
</table>

*Good = normal, −, del(5q), del(20q); Intermediate = other karyotypic abnormalities; Poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.
†Hb < 10 g/dL; ANC < 1500/μL; platelets < 100,000/μL.

Total Score:

<table>
<thead>
<tr>
<th>Risk</th>
<th>Low</th>
<th>Intermediate I</th>
<th>Intermediate II</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival, yrs</td>
<td>5.7</td>
<td>3.5</td>
<td>1.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>


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**IPSS-R: Revised June 2012**

1. New marrow blast categories
   - ≤ 2, >2 - ≤ 5, > 5 - 10, > 10 - 30%
2. Refined cytogenetic abnormalities and risk groups
   - 16 (vs 6) specific abnormalities, 5 (vs 3) subgroups
3. Evaluation of depth of cytopenias
   - clinically and statistically relevant cut points used
4. Inclusion of differentiating features
   - Age, Performance Status, ferritin, LDH, Beta-2 microglobulin
5. Prognostic model with 5 (vs 4) risk categories
   - improved predictive power


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**IPSS-R: Prognostic Score Variables**

<table>
<thead>
<tr>
<th>P.Variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very Good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM Blast %</td>
<td>≤ 2</td>
<td>&gt;2-5%</td>
<td>5-10%</td>
<td>&gt;10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
<td>8-10</td>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
<td>50-100</td>
<td>&lt;50</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>
<td></td>
</tr>
</tbody>
</table>

**IPSS-R: Prognostic Risk Categories/Scores**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>≤ 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>

High risk


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**Mutation Profiling**

- Powerful tool
  - Diagnose disease (from aging to MDS to AML)
- Prognostic:
  - Risk of Progression
  - IPSS, IPSS-R and now IPSS-R-M
- Predictive
  - Chemo and BMT response/non-response
- Targeted therapies
  - SF3B1/TET2/IDH1/IDH2/FLT3
CHIP as a Precursor State to Hematological Neoplasms

Clonal Hematopoiesis of Indeterminate Potential
Clonality Dysplasia Cytopenias Blasts

Steenema, D. Mayo Clinic Proceedings. 2015. 969-83

Unique Mutation Profile Helps Identify/Confirm Disease

- SF3B31 and JAK2: RAEB-T
- TET2, SRSF2, DNMT3A, ASXL1, SETBP1: CMML
- SRSF2, SF3B1, U2AF1, ASXL1, EZH2, BCOR, STAG2 can be highly specific for secondary AML (as compared to de novo AML)
- DDX41: Identify novel germline/inherited disorders


New Model: IPSS-Rm

- Total of 508 MDS patients from 2000-2012
  - 333 as training set
  - 175 as validation set
- Use age, IPSS-R, and mutation data
- Dynamic modification of IPSS-R to enhance predictive ability in MDS patients regardless of initial/subsequent therapy at any time in disease course


Somatic Mutations Are Associated With Disease Risk and MDS Subtype


Somatic Mutations Are Associated With Disease Risk and MDS Subtype

Survival: MDS

<table>
<thead>
<tr>
<th>MDS</th>
<th>IPSS Score</th>
<th>Risk Group</th>
<th>Median Survival (Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>Low</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>0.5-1</td>
<td>Int-1</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>1.5-2</td>
<td>Int-2</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>&gt;2</td>
<td>High</td>
<td>0.4</td>
</tr>
</tbody>
</table>

## Survival: MDS

<table>
<thead>
<tr>
<th>IPSS Score</th>
<th>Risk Group</th>
<th>Median Survival (Yrs)</th>
<th>Stage</th>
<th>Median Survival (Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
<td>Ia</td>
<td>8</td>
</tr>
<tr>
<td>0.5-1</td>
<td>Int-1</td>
<td>3.5</td>
<td>Ila</td>
<td>5.4</td>
</tr>
<tr>
<td>1.5-2</td>
<td>Int-2</td>
<td>1.2</td>
<td>Illa</td>
<td>2.4</td>
</tr>
<tr>
<td>&gt;2</td>
<td>High</td>
<td>0.4</td>
<td>IV</td>
<td>1.2</td>
</tr>
</tbody>
</table>


## IPSS-R: Survival by Risk Category

### THESE PATIENTS UNTREATED

![Survival Graph](Greenberg PL, et al. Blood. 2012;120:2454-2465.)

## What Does MDS Look Like?

**Clinician’s perspective…**

## Physician Survey Data

- Questionnaires completed by 101 docs
  - Geographically representative
  - Took place over 1.5 year period from 2005-07
- 4514 surveys returned
  - $30 incentive for completing each survey

Sekeres et al. J National Cancer Inst 2008;100:1542

## U.S. MDS Characteristics

<table>
<thead>
<tr>
<th>Age (median)</th>
<th>Newly diagnosed</th>
<th>Established</th>
</tr>
</thead>
<tbody>
<tr>
<td>71 years</td>
<td>72-75 years</td>
<td></td>
</tr>
</tbody>
</table>

| Sex (mean) | Newly diagnosed (Established) | 55% (51-57%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of MDS (median)</th>
<th>13-16 months</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>MDS Status</th>
<th>Primary</th>
<th>88 – 93%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>7 – 12%</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>Chemotherapy</td>
<td>55 – 90%</td>
</tr>
<tr>
<td>Cause</td>
<td>Radiation</td>
<td>0 – 21%</td>
</tr>
<tr>
<td>Cause</td>
<td>Chemical exposure</td>
<td>2 – 9%</td>
</tr>
</tbody>
</table>

Sekeres et al. J National Cancer Inst 2008;100:1542
U.S. MDS Characteristics

- Median Hgb: 9.1 g/dl (IQ range 8-10)
- Median Plt: 100,000/mm$^3$ (IQ range 56-151)
- Median ANC: 1780/mm$^3$ (IQ range 1070-2800)
- Circulating Blasts: 1-5%: 16%
  >5%: 10%

Sekeres et al. J National Cancer Inst 2008;100:1542

Transfusion Burden of MDS Patients

MDS Patient Survey

- A self-directed, online survey of MDS patients conducted over a 2-week period in March 2009
  - Sponsored by the AA & MDS Intl. Foundation
  - MDS pts registered with the AA & MDS Intl. Foundation

- N = 358 people from 46 states
- Results were presented at ASH, December 2009

Who Took the Survey?

- Average age: 65 years old
- Gender: 51% women, 49% men

How Long Did It Take to Get an MDS Diagnosis?

- First abnormal blood test
- Diagnosis of MDS: 3 years

Sekeres et al. ASH 2009; abstract 1771.
How Doctors First Describe MDS

- Hematologic malignancy: 80%
- Leukemia: 56%
- Cancer: 12%
- Other: 12%
- Thrombocytopenia: 17%
- Neutropenia: 17%
- Anemia: 11%
- Syndrome: 7.5%
- Blood disorder: 7%
- Leukemia: 4%

Percent of total responses
Sekeres et al. ASH 2009; abst. 1771

What’s My Risk?

- Low risk: 13%
- Int-1: 18%
- Int-2: 11%
- High: 4%
- Don’t know: 55%

IPSS Risk Score
Sekeres et al. ASH 2009; abst. 1771

What’s My Prognosis?

Percentage of MDS patients who never discussed life expectancy with their doctor

- All patients: 35%
- Lower-risk patients: 33%
- Higher-risk patients: 19%

Conclusions: MDS Biology

- MDS is a complex group of bone marrow malignancies that result in marrow failure
  - MDS is rare – but growing cancer
  - Challenging to diagnosis
  - Marrow testing critical to obtain information
    - Morphology, cytogenetics, molecular profiles
  - Important to understand your disease prognosis and implications for therapy
  - IPSS – starting point for risk stratification

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
  - OR
  - Trilineage marrow improvement
Treatment Options for LR-MDS

- Observation/Watch and Wait
- Supportive Transfusions (RBC and platelets)
- Iron Chelation
- Hematopoietic Growth Factors
- Immunosuppressive Therapy (ATG, cyclosporine)
- Immunosomulatory Drugs (Lenalidomide)

Medications Used for MDS

**FDA Approved**
- HMT
  - Azacitidine
  - Deoxyazaadcinde
- Immunomodulatory
  - Lenalidomide
- Iron chelators
  - Desferasirox
  - Deferoxamine
  - Deferiprone

**Approved Other Indications**
- Growth Factors
  - Epotin alfa/Darbepoetin alpha
  - Filgrastim (G-CSF)
  - Sargramostim (GM-CSF)
  - Romiplostim (Nplate)
  - Eltrombopag (Promacta)
- Immunosuppressive
- Thalidomide
- Chemotherapy/SCT

What are Hematopoietic Growth Factors?

- Synthetic versions of proteins normally made in the body to stimulate growth of red cells, white cells and platelets
  - Promote growth and differentiation
  - Inhibitors of apoptosis (cell death)
- RED CELL Growth Factors
  - Erythropoietin (EPO, Procrit®, Epogen®)
  - Darbepoetin (Aranesp®)
- WHITE CELL Growth Factors
  - Granulocyte colony stimulating factor (GCSF, Neupogen®)
  - Granulocyte-macrophage colony stim factor (GM-CSF, Leukine®)
  - Pegfilgrastim (Neulasta®)
- PLATELET Growth Factors
  - Thrombopoietin (TPO, romiplostim, Nplate®)

- Note, these are not FDA-approved for MDS

Problem with EPO

- 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 patients
- Has had major effects on insurance coverage

Patient Selection for ESA

- Good response (74%, n=34)
- Intermediate response (23%, n=31)
- Poor response (7%, n=29)

Stimulating White Blood Cells and PLTS

- **White Cell Growth Factors**: Not routine - DON'T treat the number, treat the patient
  - Active infections - recurrent/resistant infections
  - Neutropenic fever
  - Can be combined with red cell growth factors to improve responses in some patients
  - Side effects: fever, bone pain, injection site reactions
  - Does stimulating white blood cells cause leukemia

- **Platelet Growth Factors**: Not routine - Don't treat number, treat the patient
  - Bleeding history - Single digit plts
  - Romiplostim: Azacitidine Rx pts Romiplostim vs placebo
  - Less bleeding events
  - Does stimulating platelets cause leukemia??

Lenalidomide: Pharmacologic Evolution

- More "potent" immunomodulator than thalidomide
- Up to 50,000 times more potent inhibitor of TNFα
- 3-5 fold stimulation of T-cell proliferation, IL-2 and IFNγ production
- Anti-angiogenesis impact

Seiler J. Semin Oncol 2001; 28:202
Data on file: Summit, NJ: Celgene Corporation 2005

Lenalidomide MDS - 003 Study Design

Eligibility
- del 5q
- ≥2U RBC/8wks
- T6 weeks Ht Platelets >50/10^9
- ANC >500/10^9
- Low/Int-1 Risk

10 mg po qd
- Yes → Continue

10 mg po x21
- No → Off Study

Primary Endpoint: Transfusion-Independence [Hgb >1g/dl]
Secondary: Cytogenetic response, Path Response

List et al. NEJM 2005

MDS-002/003: Intent to Treat Erythroid Response at 24 wk (Preliminary Report)

- Transfusion indep
- Median duration of transfusion independence
- Median time to response


Kaplan-Meier Estimate of the Duration of Independence from Red-Cell Transfusion

Treatmnet GOALS in MDS

- Improve marrow function
- Decrease transfusion Needs
- Decrease impact of MDS on QOL
- Establish careful monitoring plan

Low IPSS
INT-1 IPSS
INT-2 IPSS
High IPSS

- Stabilize marrow function
- Lower risk transformation
- Move to definitive therapy
- Trilineage marrow improvement

Treatment Options for HR-MDS

- Azacitidine (Vidaza) or Decitabine (Dacogen)
- Lenalidomide (Revlimid)
- Intensive Chemotherapy
- Bone Marrow Transplant
- Clinical Trials

Epigenetics

Change in gene expression which is heritable and does not involve a change in DNA sequence (not genetic):
Could inactivate tumor suppressor genes according to Knudson two-hit hypothesis:

Pathway for the Methylation of Cytosine in the Mammalian Genome and Effects of Inhibiting Methylation with 5-Azacytidine

Hypomethylating Agents

Structural Differences

Herman JG, Baylin SG. NEJM 2003;349:2042-54.

Pathway for the Methylation of Cytosine in the Mammalian Genome and Effects of Inhibiting Methylation with 5-Azacytidine

Herman JG, Baylin SG. NEJM 2003;349:2042-54.

CALGB #9221 Trial Design

A Randomized Phase III Controlled Trial of Subcutaneous Azacitidine in Myelodysplastic Syndromes

Silverman L. et al. JCO 2002
**Time to AML Transformation**

- **Azacitidine**
- **Supportive Care**

**Probability of Remaining Event-Free**

- **P=0.001**
- **p=0.007**

*Silverman L, et al. JCO 2002*

**Azacitidine Survival Study (AZA-001)**

- **5AC 75 mg/m² d x 7 d q28 d (n=179)**
- **Conventional care regimens**
  - Best Supportive Care (BSC) (n=105)
  - Low Dose Ara-C (LDAC, 20 mg/m²/d x 14 d q28-42 d) (n=49)
  - Std Chemo (7 + 3) (n=25)

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

*Fenaux P, et al. Blood. 2007*

**Overall Survival: Azacitidine vs CCR**

- **Log-Rank p=0.0001**
- **HR = 0.58 [95% CI: 0.43, 0.77]**
- **CR=17%; ORR=35%**
- **Difference: 9.4 months**


**Decitabine (EORTC) Phase III MDS Trial Study Design**

- **Decitabine + Supportive Care**
  - 15mg/m² over 3 hours q8h x 3days 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**


**EORTC: Overall Survival**

- **Median (months): 10.1 vs 8.5**
- **HR = 0.88, 95% CI (0.66, 1.17)**
- **Logrank test: p=0.35**

*Wijermans P, Lubbert M, Suciu S, et al. ASH, December 6-9, 2008*

**Azacitidine/Decitabine**

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

*List A, NEJM 2006; 355: 1456-65*
## HMT Alone in MDS/AML

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dose (mg/m²)</th>
<th>Schedule</th>
<th>Eval Pts. N</th>
<th>CR N (%)</th>
<th>ORR (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wijermans 2000</td>
<td>DAC: 15</td>
<td>IV Q8x 3d</td>
<td>66</td>
<td>20%</td>
<td>49%</td>
<td>15mo mOAS</td>
</tr>
<tr>
<td>Silverman 2002*</td>
<td>SAC: 75</td>
<td>SC x 7d</td>
<td>191</td>
<td>21%</td>
<td>60%</td>
<td>18mo mOAS</td>
</tr>
<tr>
<td>Kantarjian 2006*</td>
<td>DAC: 15</td>
<td>Q8 IV x3d</td>
<td>170</td>
<td>17%</td>
<td>30%</td>
<td>14 mo mOAS</td>
</tr>
<tr>
<td>Steensma 2009</td>
<td>DAC: 20</td>
<td>IV x 5d</td>
<td>99</td>
<td>32%</td>
<td>51%</td>
<td>19.4mo mOAS</td>
</tr>
<tr>
<td>Blum 2010</td>
<td>DAC: 30</td>
<td>IV x 10d</td>
<td>53</td>
<td>64%</td>
<td>13.8 mo OAS</td>
<td></td>
</tr>
<tr>
<td>Fenaux AZA-001</td>
<td>SAC: 75</td>
<td>IV x 7d</td>
<td>179</td>
<td>29%</td>
<td>78%</td>
<td>24.5mo OAS</td>
</tr>
<tr>
<td>Lubbert 2012</td>
<td>DAC: 15</td>
<td>IV Q8s 3d</td>
<td>227</td>
<td>26%</td>
<td>5.5mo OAS</td>
<td></td>
</tr>
<tr>
<td>Garcia-Manero 2013</td>
<td>DAC: 20</td>
<td>D1-3 vs D1,8,15</td>
<td>65</td>
<td>16%</td>
<td>23%</td>
<td>D1-3 best</td>
</tr>
</tbody>
</table>

## Limited Options for Pts Failing HMT
- Increase HMT dose or exposure
  - SGI-110 (block deamination/breakdown of HMT drug)
- Switch to alternate HMT agent
- Combination therapy
  - HDACi, chromatin modifier or immunomodulatory agent
- Induction chemotherapy
- Stem cell transplant/RIC or nonmyeloablative
- Clinical Trial


## BMT: How To Decide
- Insurance coverage?
- Is there a donor?
- Need to balance the risk of disease progression to risk of treatment (infection/GVHD, organ damage, death)
- Is the patient strong/fit enough for BMT?
  - How to evaluate/Comorbidity Index/Age


## Cure: Bone Marrow Transplant
- Allogeneic HCT offers long term DFS for pts with MDS (30-50%)
- Decreased ability to offer HCT due to comorbidities (not age per se)
- Optimize Performance Status/QOL

“BOSTON STRONG”
Colleen Slime, Age 81 Boston Marathon, 2015

## What Pre-Transplant Therapy is Best?
- Cytoreduction/Control disease
  - HMT vs Induction chemotherapy vs None
  - No definitively superior approach
  - Allow time for maximal GVL effect
- Ongoing prospective studies
  - Knöger/Platzbecker (SAC alone vs SAC to RIC)
  - EORTC 1301 (10d DAC to BMT vs 3+7 to BMT)
  - BMT CTN 1102 (HMT alone vs HMT to RIC-BMT)
- When to proceed with HCT/timing?


## MDS Disease Burden Pre-HCT and Relapse Risk Post-HCT

Cytogenetic Risk and Relapse Post Transplant

![Graph showing probability of relapse for different cytogenetic risk categories: Very Good (n=13), Good (n=46), Intermediate (n=175), Poor (n=148), Very Poor (n=97).]


HCT Decision Analysis

<table>
<thead>
<tr>
<th>IPSS RISK</th>
<th>Estimated Life expectancy (years) after HCT for MDS (age &lt; 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Immediate HCT</td>
</tr>
<tr>
<td>Low</td>
<td>6.51</td>
</tr>
<tr>
<td>Int-1</td>
<td>4.61</td>
</tr>
<tr>
<td>Int-2</td>
<td>4.93</td>
</tr>
<tr>
<td>High</td>
<td>3.20</td>
</tr>
</tbody>
</table>


HCT: Decision Analysis, RIC

<table>
<thead>
<tr>
<th>Estimated Life expectancy (years) after RIC-HCT for MDS (age ≥ 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low/Int-1</td>
</tr>
<tr>
<td>Overall LE</td>
</tr>
<tr>
<td>QALE: TI</td>
</tr>
<tr>
<td>QALE: TD</td>
</tr>
<tr>
<td>Int-2/High</td>
</tr>
<tr>
<td>QALE: HR-MDS</td>
</tr>
<tr>
<td>QALE: GvHD</td>
</tr>
</tbody>
</table>

Koreth et al. JCO 2013;31:2662

ASBMT/EBMT: Panel Recommendations

- Early HCT for higher-risk MDS and poor-risk lower risk MDS
- No rec for pre-HCT induction chemo/HMT
- No rec for related vs unrelated donor
- No rec for RIC vs high-dose conditioning

Ofarsky et al. BBMT 2009;15:137

Conclusions

- Effective therapy for MDS exists
  - IPSS and IPSS-R; starting point risk stratification
  - Important to set goals of therapy
- Growth factors, transfusions, Len to ↓ transfusions
- Epigenetic tx for high risk and 5AC improves OAS
- Allogeneic HCT offers cure but also toxicity
- Future trials will incorporate molecular mutations for prognostic models to individualize therapy and to inform treatment decisions upfront

Thank you

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