Learning Objectives:
• Understand key disease characteristics needed to facilitate diagnosis, staging, and tailored treatment of MDS and Acute Leukemia
• Define individualize treatment goals
• Examine new treatment approaches
• Delineate how treatment strategies fit into current NCCN treatment algorithms
• Discuss how a comprehensive targeted treatment plan may improve overall and transplant outcomes

Characterizing MDS

Definition:
• A group of clonal bone marrow stem cell disorders, characterized by hypercellular marrows, peripheral cytopenias, and cell functional abnormalities
  – Ineffective hematopoiesis
• Heterogeneity: highly variable natural history
  • High mortality rate
• Unless permanent control achieved (by alloBMT) death due to bone marrow failure, with or without conversion to AML

http://www.hmds.org.uk/mds.html

Age-related Incidence of MDS

Predisposition:
- Acquired:
  • Senescence
  • Mutagen/Genotoxic Stress
  - Therapeutic alkylators, Topo-II agents, β-emitters (32P), autoSCT
  - Environmental/occupational (benzene)
  • Tobacco
  • Aplastic anemia
  • PNH

- Heritable:
  • Constitutional genetic disorders
  - Trisomy 8 mosaicism
  - Familial monosomy 7
  • Neutrophilic variants
  • Embryonal dysgenesis (del12p)
  • Congenital Neutropenia
  • Kostmann, Schwachman-Diamond
  • DNA repair deficiencies
  • Fanconi anemia, AT, Bloom syndrome
  • Pharmacogenomic polymorphisms
    (GSTq1-null)


Clinical Overlap / Associations:
• AML
• Aplastic anemia
• Myeloproliferative disease
• LGL leukemia
• Autoimmune diseases

With Permission of J Maciejewski,M.D. Taussig Cancer Center/ Cleveland Clinic Foundation
With Permission of American College of Physicians/Syracuse Postgraduate Medical School
With Permission of American College of Physicians/Cleveland Clinic Foundation
ACP not responsible for accuracy of figure translation.
**Diagnosis and Classification:**

Basic Diagnostic Evaluation:

- Peripheral blood counts + reticulocyte count
- Bone marrow biopsy and aspiration
  - Cytogenetics
- Auxiliary tests
  - FISH
  - Flow cytometry in indeterminate cases
  - Iron saturation, ferritin
  - B12, folate levels
  - EPO level

Establish diagnosis

Assess

FAB/WHO classification

- IPSS score (if applicable)

http://www.NCCN.org MDS Guidelines

http://www.hmds.org.uk/mds.html

**WHO Reclassification of FAB MDS Subtypes**

<table>
<thead>
<tr>
<th>MDS (FAB)</th>
<th>MDS (WHO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory Anemia (RA) &lt;5% Blasts</td>
<td>Refractory Anemia (RA)</td>
</tr>
<tr>
<td>Refractory cytopenias with multilineage dysplasia (RCMD)</td>
<td>Refractory cytopenias with multilineage dypleasia and ringed sideroblasts (RCMD-RS)</td>
</tr>
<tr>
<td>MDS: Unclassifiable (MDS-U)</td>
<td>MDS with isolated del(5q): Sq minus syndrome</td>
</tr>
<tr>
<td>RA with &gt;15% ringed sideroblasts</td>
<td>RA with excess blasts I (RAEB-I): 5-10% blasts</td>
</tr>
<tr>
<td>RA with excess blasts-II (RAEB-II): 11-20% blasts</td>
<td>RA with excess blasts in transformation (RAEB-t): 21-30% blasts</td>
</tr>
<tr>
<td>RA with excess blasts-I (RAEB-I): 5-10% blasts</td>
<td>RA with excess blasts-II (RAEB-II): 11-20% blasts</td>
</tr>
<tr>
<td>RA with excess blasts in transformation (RAEB-t): 21-30% blasts</td>
<td>Acute myeloid leukemia</td>
</tr>
</tbody>
</table>

**IPSS Score**

Prediction of Survival

Prediction of AML

WIPSS Score

Prediction of Survival

Prediction of AML

Time dynamic risk assessment

Uses WHO diagnoses

Accounts for transfusion need
**Goals of Therapy**

- PROLONG SURVIVAL
- Select Therapy best suited for the individual
- Minimize toxicity
- Improve blood counts
  - Decrease transfusion
  - Decrease infections
- Improve quality of life

**Immunotherapy (IP): Identify Responding Subsets**

**Rationale:**
A subset of MDS patients have a component of immune attack contributing to their cytopenias

**Supportive Evidence:**
In four studies, 29% (34/115) response to equine ATG. Rabbit ATG: RR 42%. 75% responders durable response (median 31.5 months).

**Candidates:**
- HLA-DR-15-positive
- RA (<5% blasts)
- Age <60
- Brief transfusion history
- Trisomy 8 abnormality
- Normal cytogenetics
- IPSS Low/Int-1
- Marrow cellularity <30%

**Lenalidomide in 5q Deletion:**

**Phase II Study Design**

Eligibility: del(5q); IPSS low or Int-1; platelets > 50K/mm$^3$; neutrophils > 500/mm$^3$; transfusion dependent

**Lenalidomide: Efficacy**

<table>
<thead>
<tr>
<th>Complexity</th>
<th>n</th>
<th>CyResponse</th>
<th>CcyR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sq: only</td>
<td>64</td>
<td>77%</td>
<td>45%</td>
</tr>
<tr>
<td>Sq: plus one</td>
<td>15</td>
<td>67%</td>
<td>40%</td>
</tr>
<tr>
<td>Sq: plus two</td>
<td>6</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Lenalidomide: Adverse Events (N = 148)**

<table>
<thead>
<tr>
<th>All Patients del(5q)</th>
<th>All Grades, %</th>
<th>2 Grade 3, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>(62)</td>
<td>(50)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>(59)</td>
<td>(53)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>(49)</td>
<td>(3)</td>
</tr>
<tr>
<td>Dose modifications</td>
<td>118 (80)</td>
<td>(5)</td>
</tr>
<tr>
<td>Final dose (5 mg qd or qod)</td>
<td>108 (72)</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to AEs</td>
<td>32 (22)</td>
<td></td>
</tr>
<tr>
<td>Deaths on study</td>
<td>10 (7)</td>
<td></td>
</tr>
<tr>
<td>Suspected drug-related by investigator</td>
<td>3 (1.4)</td>
<td></td>
</tr>
</tbody>
</table>
Revlimid in non-5q MDS patients

- 214 patients with > 2 years followup
  - 78% Low/Int 1
- 26% response to RBC TI (median 4.8 weeks)
  - Duration 41 weeks (8-136.4)
  - Median hgb rise 3.2 g/dl
- 17% had 50% reduction in PRBC needs
- Overall RBC TI RR 43%
- TI occurred in non-5q without clonal suppression
- Response seen in patients >2U PRBC/mo
- “Revlimid restores erythropoietic activity to the MDS clone”

Raza et al Blood Epab Sept 24 2007

Mechanism of Action
DNMTs

DNA Methyltransferase Inhibitors (MTIs)

DNA Methyltransferase Inhibitors

Azacitidine
5-azacytidine

RNA

Decitabine
5-aza-2’-deoxycytidine

DNA

AZA-001: Trial Design

Physician Choice of 1 of 3 Conventional Care Regimens
1. BSC only or
2. LDAC or (20 mg/m² SC x 14d x 2-42d)
3. 7+3 chemotherapy (induction + 1 or 2 consolidation cycles)

Stratify:
- FAB = RAEB, RAEB-T
- IPSS = INT-2, High

VIDAZA® + BSC (75 mg/m² x 7d SC q28d) N=179

CCR N=179

Treatment continued until unacceptable toxicity or AML transformation or disease progression

AML=acute myeloid leukemia; BSC=best supportive care; CCR=conventional care regimen; IPSS=international prognostic scoring system; LDAC=low-dose Ara-C

AZA-001 Trial: VIDAZA® Significantly Improves Overall Survival (OS)

Log-rank, P=0.0001
HR=0.58 (95% CI: 0.43-0.77)

15 months
24.5 months

VIDAZA CCR

Cl在意の信頼区間; HR=危険率, ITT=intent-to-treat
AZA-001 Trial: Survival Results

- VIDAZA® provided a significantly improved OS compared with CCR in the ITT population (log-rank \( P=0.0001 \))
- VIDAZA median OS was 24.5 months compared with 15 months for CCR
- VIDAZA 2-year OS was 51% compared with 26% for CCR (24.6% difference, 95% CI, 13.1-36.1)
- The relative risk of death was 0.58 (95% CI: 0.43-0.77), indicating a 42% less risk for the VIDAZA group relative to the CCR group
- More deaths were observed on CCR (113) compared with VIDAZA (82)

AZA-001: First Occurrence of Treatment Emergent Hematologic AEs with VIDAZA®

- Thrombocytopenia
- Neutropenia
- Anemia

Decitabine Phase III MDS Trial: Efficacy

- Overall response (IWG criteria), %: 17 vs 9
- CR, %: 9 vs 0
- PR, %: 8 vs 0
- Hematologic improvement (IWG), %: 13 vs 7
- Median time to response (CR + PR), mo: 3.2 (95% CI: 2.5-3.8) vs N/A
- Median duration of response (CR + PR), mo: 9.8 (95% CI: 7.5-12.2) vs N/A
- Median time to AML/death, mo: 12.1 vs 7.8

Decitabine Phase III MDS Trial: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Decitabine, % (n = 83)</th>
<th>Supportive Care, % (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Grade 3: 10, Grade 4: 77</td>
<td>Grade 3: 25, Grade 4: 25</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 3: 22, Grade 4: 63</td>
<td>Grade 3: 27, Grade 4: 16</td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade 3: 11, Grade 4: 1</td>
<td>Grade 3: 14, Grade 4: 1</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>Grade 3: 17, Grade 4: 6</td>
<td>Grade 3: 4, Grade 4: 0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Grade 3: 13, Grade 4: 2</td>
<td>Grade 3: 7, Grade 4: 2</td>
</tr>
</tbody>
</table>

Median number of courses: 3
52% received ≥3 courses
26% received ≥6 courses

Decitabine Phase III MDS Trial Study Design

- Open-label, multicenter, 1:1 randomized study
- IPSS: Int-1, Int-2, and high-risk MDS patients eligible
- Primary end points: response, time to AML/death
  - IWG response criteria utilized for assessment

Decitabine Phase III MDS Trial: What Drug, What Patient?

- Transfusion/CSF support: RARS, EPO for low serum EPO levels at dx
  - EPO/G if <2U PRBC/mo
- IP therapy & hypoplastic, IPSS low, minimal transfusion burden
  - Revlimid: 5q cytogenetics, IPSS low/int-1, RBC response only
    - Best if <4 PRBC/Cycles
  - Trisenox: Low IPSS risk patients failing prior therapy-third line drug
- Dacogen: possibly as bridge for secondary AML
- Vidaza: All FAB types, including CMML, all IPSS scores, use early when intervention required
  - Maintenance concept: able to use indefinitely
Bone Marrow Transplantation

Remission Durability Requires Stem Cell Directed Therapy

Approximation of Life Expectancy (Years)

<table>
<thead>
<tr>
<th></th>
<th>Immediate Transplant</th>
<th>Transplant in 2 Years</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>


NEW AGENTS ON THE HORIZON...

To view the most recent and complete version of the NCCN Acute Leukemia and MDS Clinical Practice Guidelines in Oncology (Version 2.2007), go online to www.nccn.org.
NEW AGENTS ON THE HORIZON...

<table>
<thead>
<tr>
<th>New Agents</th>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD4028</td>
<td>Kinase inhibitor</td>
<td>Inhibits Aurora kinase (AUR) inhibitor</td>
</tr>
<tr>
<td>GSK2118872</td>
<td>IR/PI3K AMPK kinase inhibitor</td>
<td>Inhibits IR/PI3K AMPK kinase inhibitor</td>
</tr>
<tr>
<td>AEE788</td>
<td>PCM105</td>
<td>Inhibits PCM105</td>
</tr>
<tr>
<td>VX-680</td>
<td>BRAF inhibitor</td>
<td>Inhibits BRAF kinase</td>
</tr>
<tr>
<td>LAG-3</td>
<td>PD-1/PD-L1 inhibitor</td>
<td>Inhibits PD-1/PD-L1 pathway</td>
</tr>
<tr>
<td>JNJ-54904272</td>
<td>PD-L1 inhibitor</td>
<td>Inhibits PD-L1 pathway</td>
</tr>
<tr>
<td>ALIZ8</td>
<td>TGF-βRI inhibitor</td>
<td>Inhibits TGF-βRI pathway</td>
</tr>
<tr>
<td>Remarks</td>
<td></td>
<td>- Various agents with potential anti-cancer properties</td>
</tr>
</tbody>
</table>

NEW AGENTS ON THE HORIZON...

<table>
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<tr>
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<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG-120, AG-221</td>
<td>Altered cell metabolism</td>
<td>Inhibits dehydrogenase 1 and 2 (DH1 and DH2) inhibitors</td>
</tr>
<tr>
<td>Conurete Q300 and L-arginine</td>
<td>Altered intracellular metabolism and electron transport chain</td>
<td></td>
</tr>
<tr>
<td>CPB13</td>
<td>Induction of peroxisome dehydrogenase and ketoglutarate dehydrogenase</td>
<td></td>
</tr>
<tr>
<td>INC024909</td>
<td>Indoleamine 2,3-dioxygenase (IDO) inhibitor</td>
<td></td>
</tr>
</tbody>
</table>

Cytotoxic agents / cell cycle inhibitors
- Cytotoxic agents (A-CIA) | Nucleoside analogues, nucleotide analogues, and phosphorodiolates |
- Olaparib (ABT-835) | Inhibits poly(ADP-ribose) polymerase (PARP) |
- Sorafenib (S951) | Inhibits Raf and MEK kinases |
- Olaparib (S951) | Quinolin-2(1H)-one derivatives, replication-dependent DNA damage agents |