MDS and Elderly AML

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Myelodysplastic Syndrome

- Incidence/Prevalence
- WHO Categories
- International Prognostic Scoring System (IPSS)
- Treatment and Goals of Therapy
- Response Criteria
Myelodysplastic Syndromes

- Clonal hematopoietic stem cell diseases
- Peripheral cytopenia(s) in one or more cell lines
  - Anemia
  - Neutropenia
  - Thrombocytopenia
- Dysplasia in one or more myeloid precursors
- Ineffective hematopoiesis
MDS Epidemiology

- Median onset: 70 years old
- 10,300 new cases in the US per year
- Increased incidence of AML
- Major morbidity and mortality from bone marrow failure
  - Bleeding
  - Infections
  - Iron overload from multiple PRBC transfusions
WHO Categories

- Refractory cytopenia with unilineage dysplasia
  - Refractory anemia/neutropenia/thrombocytopenia
- Refractory anemia with ringed sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anemia with excess blasts
  - RAEB-1: 5-9% BM blasts
  - RAEB-2: 10-19% BM blasts
- MDS-unclassified
- MDS with isolated del(5q)
Workup and Testing

- CBC, differential, peripheral blood smear
- Bone marrow exam
- Cytogenetics
- B12, folate
- Erythropoietin level
- Transfusion history
- HLA typing if transplant candidate
Figure 2. Megaloblastic erythroid precursors seen on MDS display an "open" conformation of chromatin (MacNeal Tetrachrome 1000x)
Figure 3. Micromegakaryocyte seen in the bone marrow aspirate of a patient with MDS displays hypolobulation of the nucleus

Maslak, P. ASH Image Bank 2002;2002:100458
Figure 1. Classic appearance of a ring sideroblast shows iron deposition in a "necklace" around the nucleus

Maslak, P. ASH Image Bank 2005;2005:101383
IPSS Scoring System

Cytopenia definitions

Hgb < 10 g/dL
Neutrophils < 1800/uL
Platelets < 100,000/uL

Table 1. International Prognostic Scoring System (IPSS): prognostic variables

<table>
<thead>
<tr>
<th>Marrow blasts, %</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>&lt;5</td>
<td>5-10</td>
<td>—</td>
<td>11-20</td>
<td>21-30</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Karotype</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td>—</td>
</tr>
</tbody>
</table>

— indicates not applicable; Good = normal, -y, del(5q), del(20q); Poor = complex (≥3 abnormalities) or chromosome 7 anomalies; and Intermediate = any other abnormalities.

Table 2. International Prognostic Scoring System (IPSS): clinical outcomes

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Total score</th>
<th>Median survival, y</th>
<th>Time for 25% to progress to AML, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5-1.0</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5-2.0</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>High</td>
<td>≥ 2.5</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Nimer, Blood, 2008
IPSS Shortcomings

- Degree of cytopenia is undervalued
- Contrast two example patients
- Patient A: IPSS score 0.5
  - Normal cytogenetics, 4% blasts, hemoglobin 9, platelets 1000, neutrophils 200
- Patient B: IPSS score 2.0
  - Normal cytogenetics, 11% blasts, hemoglobin 9, platelets 98,000, neutrophils 2400
- Which patient is in more dire circumstances?
Goals of Therapy

- Cure? Allo transplant for appropriate patients
- Reduction of transfusion requirements
- Improved platelet or neutrophil counts
- Delaying onset of AML
Treatment Options

- Transfusions and antibiotics
- Hematopoietic growth factors
  - Erythropoietin, G-CSF
- Transcriptional modifying therapy
  - Re-expression of genes needed for hematopoiesis
  - Hypomethylating agents: 5-azacytidine, decitabine
  - HDAC inhibitors: PXD101, other clinical trials
- Lenalidomide: approved for del(5q) MDS
- Allogeneic stem cell transplantation
Treatment for Low/Int-1 Risk

- Anemia symptoms predominate
  - 5q-: Lenalidomide
  - Epo < 500 mU/mL: Erythropoietin +/- GCSF
  - Epo > 500 mU/mL: Azacytidine/decitabine
  - Hypocellular marrow, HLA-DR15, or PNH clone
    - Consider immunosuppression with ATG and cyclosporine

- Thrombocytopenia/neutropenia predominate
  - Azacitidine/decitabine
Clinical Trial Data: 5q- Syndrome

- Lenalidomide 10mg PO either 21 days or continuous on 28 day cycle
- 148 patients with 5q-
  - 112 had reduced tx needs
  - 99 no longer required tx
- 38 of 62 evaluable patients achieved cytogenetic remission

List, NEJM, 2006
Clinical Trial Data: Epo

- 68 MDS patients
  - 26 RA, 16 RARS, 26 RAEB
- All treated with erythropoietin
- Multiple logistic regression model showed following to be good risk prognostic factors
  - Low epo
  - Low blast count
  - Low transfusion need

Wallvik, EJH, 2002
Int-2/High Risk

- For patients who are candidates for high-intensity treatment
  - If donor available: Treat with hypomethylating agent, then transplant
  - If no donor: Hypomethylating agent versus induction-type chemotherapy

NCCN 2010
Int-2/High Risk

- For patients who are not candidates for high-intensity therapy:
  - Hypomethylating agent
  - Clinical trial
  - Supportive care

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Clinical Trial Data: Azacitidine

- Randomized to azacitidine vs. conventional care
  - Conventional care
    - Supportive care
    - Low-dose cytarabine
    - Intensive chemotherapy
  - 358 patients
    - 179 in each arm

Fenaux, Lancet Oncology, 2009
Clinical Trial Data: Azacitidine

Fenaux, Lancet Oncology, 2009
Transplantation

- Only truly curative treatment
- Patients with low/int-1 risk disease do better than int-2/high risk
- Need to weigh transplant-related complications
- Low/int-1 disease:
  - Transplant after disease progression
- Int-2/high disease:
  - Transplant as soon as a donor is identified

Stone, Blood, 2009
Transplantation

- Improved HLA typing makes well-matched MUD donors nearly as good an option as related donors
- Fewer marrow blasts lead to better outcomes
- Myeloablative conditioning
  - Higher blast counts, younger patients
- Reduced-intensity conditioning
  - Lower blast counts, older patients

Stone, Blood, 2009
Iron Chelation Recommendations

Table 3. Recommendations for initiating and monitoring iron chelation therapy in myelodysplastic syndromes.¹

MDS patients who would benefit most from treatment of iron overload
- Requiring transfusion of ≥ 2 RBC units/month for ≥ 1 year
- Ferritin level >1000 ng/mL
- Low-risk MDS
  - IPSS low or intermediate-1
  - WHO RA, RARS, and 5q-
- Life expectancy >1 year
- Without comorbidities that would limit prognosis
- Candidate for allograft
- In whom there is a need to preserve organ function
- Unresponsive to or ineligible for primary therapy such as immunomodulatory or hypomethylating agents

Monitoring Iron Overload
- Serum ferritin
- Transferrin saturation
- MRI where available
- Investigational parameters (NTBI, LPI, ROS) where available
- Monitoring of organ function (cardiac, hepatic, endocrine) where indicated
- At least every 3 months in patients receiving transfusions, following recommendations for individual ICT agents

Duration of ICT
- As long as transfusion therapy continues
- As long as IOL remains clinically relevant

Iron Chelation Options

- Deferoxamine
  - Given SC, 1-2 grams overnight, 5-7 days per week
  - Logistically challenging
  - Ear, eye, renal toxicities

- Deferasirox
  - Oral, 20 mg/kg daily
  - Expensive
  - Skin, GI, renal toxicities
Suggested Treatment Algorithm

Figure 1. Approach to therapy of MDS patients. Consider erythroid-stimulating agents in any patients with baseline (erythropoietin) less than 500 mIU/mL; add low-dose granulocyte colony-stimulating factor if no response after 8 weeks of therapy (especially if RARS [refractory anemia with ringed sideroblasts]). Consider iron chelation in selected lower-risk chronically transfused patients. DNAMTI indicates DNA methyl transferase inhibitors; and RIC, reduced intensity conditioning.
Response Criteria

- All responses must last > 4 weeks

- Complete remission
  - <5% marrow blasts, normal maturation
  - Hgb > 11, platelets > 100,000, neutrophils > 1000

- Partial remission
  - All CR criteria, except
  - >5% marrow blasts with 50% improvement
  - Cellularity and morphology are not relevant
Response Criteria

- **Stable disease**
  - Failure to achieve PR, but no progression for >8 weeks

- **Failure**
  - Death or disease progression

- **Cytogenetic response**
  - Complete: Disappearance of abnormal clone
  - Partial: > 50% reduction of abnormal clone
Response Criteria

- Hematologic improvement
  - Erythroid: Hgb increase by > 1.5g/dL (<11 baseline) and
  - Platelet: Increase by 30,000/uL (<100,000 baseline)
  - Neutrophil: Increase by 100% and > 500/uL (<1000 baseline)
“I Am Older, Not Elderly,” Said the Patient With Acute Myeloid Leukemia… (Schiffer, JCO, 2010)

Median age 70 years

Tallman, M. S. Hematology 2005;2005:143-150
AML In Older Adults

- Therapy-related or MDS-related AML more common
- Lower WBC and blast count, less proliferative
- Disease resistant to chemotherapy
- Less favorable cytogenetics
- Lower CR rates (25-50%)
- Lower 5-year survival rates (5-10%)
- Presence of comorbidities
AML Induction In Older Adults

- **Performance Status 0-2**
  - 7+3 induction, SQ cytarabine, azacitidine, decitabine, clofarabine

- **Performance Status > 2**
  - SQ cytarabine, azacitidine, decitabine, hydroxyurea

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AML Consolidation in Older Adults

- Allogeneic transplant using reduced-intensity conditioning regimen
- Repeat anthracycline + cytarabine course
- Dose-attenuated high-dose cytarabine (1-1.5g/m2)
- Azacitidine
- Decitabine

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Treatments in Development

- Cloretazine-alkylating agent
- Clofarabine-nucleoside analogue
- AC220-FLT3 inhibitor
- Tipifarnib-farnesyltransferase inhibitor
- Depsipeptide (and others)-histone deacetylase inhibitor