Role of Stem Cell Transplantation in Patients With MDS

Anastasios Raptis MD, Ph.D.
Disclosures

• Millennium
• Celgene
MDS: Biology

• Heterogeneous group of clonal acquired disorders
  – Ineffective hematopoiesis
  – Accumulation of immature progenitor cells and blasts
  – Hypercellular marrow in 80-90% of patients

• Peripheral blood cytopenias
  – Anemia in 90% of cases at diagnosis

• Dysplastic morphology

• De novo in 85% of cases or secondary

• Variable risk of progression to AML
Typical blood and marrow cell morphology in patients with MDS.
### WHO classification of MDS, 2008

<table>
<thead>
<tr>
<th>NAME</th>
<th>BM</th>
<th>Estimated pt (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory Anemia</td>
<td>Erythoid Dysplasia &gt;10%; &lt;5% blasts</td>
<td>10%-20%</td>
</tr>
<tr>
<td>Refractory Neutropenia</td>
<td>Granulocytoc dysplasia; &lt;5% blasts</td>
<td>1%</td>
</tr>
<tr>
<td>Refractory Thrombocytopenia</td>
<td>Megacaryocytic dysplasia; &lt;5% blasts</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Refractory anemia with ring sideroblasts (RARS)</td>
<td>Erythroid dysplasia; &gt;15% ring sideroblasts; 5% blasts</td>
<td>3%-11%</td>
</tr>
<tr>
<td>Refractory anemia with multilineage dysplasia (RCMD)</td>
<td>Multilineage dysplasia ± ring sideroblasts; &lt;5% blasts; no Auer rods</td>
<td>30%</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts type-1 (RAEB-1)</td>
<td>Dysplasia(s); 5%-9% blasts; no Auer rods</td>
<td>40%</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type-2 (RAEB-2)</td>
<td>Dysplasia(s); 10%-19% blasts;± Auer rods</td>
<td></td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>5q31 deletion; anemia; hypolobated megakaryocytes</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Childhood MDS, refractory cytopenia of childhood; RCC</td>
<td>&lt;5% blasts; hypocellular marrow</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>MDS unclassifiable</td>
<td>Does not fit other categories</td>
<td>?</td>
</tr>
</tbody>
</table>
EPIDEMIOLOGY

• Age is the most important risk factor
• Progressive accumulation of somatic mutations
• Median age is 70 years
• Slight male predominance
• 5q(-) syndrome is more common in women
• Familial MDS/AML with monosomy 7; 10 families
• Germline mutations in RUNX1 and GATA2 predispose to MDS
• Occupational exposure to organic solvents
Diagnostic Evaluation

• Medical history and PE
• Complete blood count, review of peripheral blood smear
• Bone marrow examination
• Vitamin B12 and folate deficiency
• HIV infection
• Copper deficiency
• Alcohol abuse
• Medications (antimetabolites)
Tabular and graphical representation (Kaplan-Meier survival analysis) of the five risk groups defined by the IPSS-R.

### IPSS-R

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Points</th>
<th>% patients (n = 7012; AML data on 6,485)</th>
<th>Median survival, years</th>
<th>Time until 25% of patients develop AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0-1.0</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
</tr>
<tr>
<td>Low</td>
<td>1.5-3.0</td>
<td>38%</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3.5-4.5</td>
<td>20%</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>5.0-6.0</td>
<td>13%</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;6.0</td>
<td>10%</td>
<td>0.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Survival also depended on patient age in a nonlinear fashion.

Using IPSS-R:
- 27% of IPSS lower risk “upstaged”
- 18% of IPSS higher risk “downstaged”

Scheinberg P, and Steensma DP ASH 2013;2013:451-480
WPSS.

(A) Prognostic Category

<table>
<thead>
<tr>
<th>Prognostic Category</th>
<th>WPSS Prognostic Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>WHO category</td>
<td>RCUD, RARS, MDS with isolated del(5q)</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Good</td>
</tr>
<tr>
<td>Severe anemia</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>RCMD</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>RAEB-1</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>RAEB-2</td>
</tr>
</tbody>
</table>

Cytogenetics are based on IPSS groups
Severe anemia defined as hemoglobin < 9 g/dL in males or < 8 g/dl in females

(B) Overall Survival From Diagnosis

Overall Survival From 24 Months

Overall Survival From 48 Months

Bejar R Hematology 2013;2013:504-510
Recurrent somatic mutations in MDS.


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Treatment

- Supportive care
- Hematopoietic growth factors
- Hypomethylating agents-DNA methyltransferase inhibitors
- Histone deacetylase inhibitors
- Immunomodulatory drugs
- Allogeneic stem cell transplant
Epigenetically active drugs

- Hypomethylating agents (IV/SC)
  - 5-azacytidine
  - Decitabine
- Histone deacetylase inhibitors (po)
  - Valproic acid
  - Phenyl butyrate, desipeptide
  - SAHA
Overall Survival: Azacitidine vs CCR

Log-Rank p=0.0001
HR = 0.58 [95% CI: 0.43, 0.77]
Deaths: AZA = 82, CCR = 113

Proportion Surviving

Time (months) from Randomization

Questions When Approaching Transplantation

- Donor selection
- Source of stem cells
- Risks and Benefits
- Importance of Comorbidities
- Cytogenetic profile
- When is the appropriate time for SCT
- Is Induction chemotherapy needed
- What conditioning intensity
Who is The Appropriate Donor?

- 719 pts with MDS, median age 58 yr (50-73)
- Median age of HLA-identical siblings 56 yr
- Median age of MUD 34 yrs
- No influence of donor age on the sibling cohort
- Age of MUD donor had significant effect on survival
- HLA-sib: OS 33%
- MUD younger than 30 yr: OS 40%
- MUD older than 30 yr: OS 24%

Kroger N Blood 2010;116:abstract 912
T-Cell–Replete HLA-Haploidentical Hematopoietic Transplantation for Hematologic Malignancies Using Post-Transplantation Cyclophosphamide Results in Outcomes Equivalent to Those of Contemporaneous HLA-Matched Related and Unrelated Donor Transplantation

Bashey A et al. JCO 2013;31:1310-1316
Cumulative incidence of nonrelapse mortality (NRM) and relapse of malignancy by donor type: (A) NRM and (B) relapse

Bashey A et al. JCO 2013;31:1310-1316
Adjusted estimated probabilities of overall and disease-free survival by donor type.

Bashey A et al. JCO 2013;31:1310-1316
Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors

Claudio Anasetti, M.D., Brent R. Logan, Ph.D., Stephanie J. Lee, M.D., M.P.H., Edmund K. Waller, M.D., Ph.D., Daniel J. Weisdorf, M.D., John R. Wingard, M.D., Corey S. Cutler, M.D., M.P.H., Peter Westervelt, M.D., Ph.D., Ann Woolfrey, M.D., Stephen Couban, M.D., Gerhard Ehninger, M.D., Laura Johnston, M.D., Richard T. Maziarz, M.D., Michael A. Pulsipher, M.D., David L. Porter, M.D., Shin Mineishi, M.D., John M. McCarty, M.D., Shakila P. Khan, M.D., Paolo Anderlini, M.D., William I. Bensinger, M.D., Susan F. Leitman, M.D., Scott D. Rowley, M.D., Christopher Bredeson, M.D., Shelly L. Carter, Sc.D., Mary M. Horowitz, M.D., and Dennis L. Confer, M.D. for the Blood and Marrow Transplant Clinical Trials Network


Survival after Randomization in the Intention-to-Treat Analysis.

Five-group cytogenetic risk classification, monosomal karyotype, and outcome after hematopoietic cell transplantation for MDS or acute leukemia evolving from MDS

Survival by 5-group cytogenetic classification.

Effect of Comorbidities on Outcome
Sorror ML, JCO 2007;25:4246-4254
## IPSS and Median Life Expectancy (Years) With and Without Transplantation

<table>
<thead>
<tr>
<th>IPSS risk</th>
<th>Without transplant Pts&lt;60yrs</th>
<th>By time of transplantation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>Risk</td>
<td>Early</td>
</tr>
<tr>
<td>0</td>
<td>Low</td>
<td>11.8</td>
</tr>
<tr>
<td>0.5-1</td>
<td>Int-1</td>
<td>5.2</td>
</tr>
<tr>
<td>1.5-2</td>
<td>Int-2</td>
<td>1.8</td>
</tr>
<tr>
<td>&gt;2</td>
<td>High</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*HLA identical siblings

[Greenberg et al 1997; Cutler et al 2004]
Myeloablative SCT

High dose CT and TBI

Recipient

Donor

HSCT

Complete Chimera
Reduced Intensity SCT

Recipient

Flu-Cy
Flu-Mel
2 Gy TBI

Donor

HSCT

± DLI

Mixed Chimera

Short GVHD Prophylaxis

Complete Chimera
 Conditioning Regimens

Required Contribution of GVT Effect

BU+CY+TBI*
BU+TBI*
CY + TBI*
FLU + AraC
BU + CY (± ATG)
BU + Melphalan
FLU + Melphalan
FLU + BU (3.2-16)
Tbi† + FLU (90-250)
Tbi†

* TBI at ≥12 Gy; † 2 Gy;
Allogeneic Transplants after Reduced Intensity Conditioning, by Donor Type, Registered with CIBMTR

Number of Transplants

- Related
- Unrelated PB/BM
- Unrelated CB

Proportion of Allogeneic Transplants with Reduced Intensity Conditioning for Different Indications
Role of Reduced-Intensity Conditioning Allogeneic Hematopoietic Stem-Cell Transplantation in Older Patients With De Novo Myelodysplastic Syndromes: An International Collaborative Decision Analysis
Monte Carlo analysis for low/intermediate-1 International Prognostic Scoring System (IPSS) myelodysplastic syndromes (MDS).

Koreth J et al. JCO 2013;31:2662-2670
Allogeneic Hematopoietic Cell Transplantation in Patients Age 60-70 Years with De Novo High-Risk Myelodysplastic Syndrome or Secondary Acute Myelogenous Leukemia: Comparison with Patients Lacking Donors Who Received Azacitididine

Uwe Platzbecker, Johannes Schetelig, Jürgen Finke, Rudolf Trenschel, Bart L. Scott, Guido Kobbe, Kerstin Schaefer-Eckart, Martin Bornhäuser, Raphael Itzykson, Ulrich Germing, Dietrich Beelen, Gerhard Ehninger, Pierre Fenaux, H. Joachim Deeg, Lionel Adès, German MDS Study Group, Cooperative Transplant Study Group, Fred Hutchinson Cancer Research Center, and Groupe Francophone des Myelodysplasies
OS and EFS among patients with MDS followed from the start of therapy according to treatment approach.
Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine

Itzykson R et al. Blood 2011;117:403-411
Prognostic variables of overall survival.

Itzykson R et al. Blood 2011;117:403-411
Prognostic score for overall survival.

Itzykson R et al. Blood 2011;117:403-411
OS according to IPSS-R score in MDS patients treated with AZA with a median follow-up time of 41.4 months.

Lamarque M et al. Blood 2012;120:5084-5085
Considerations of when to proceed to an allogeneic HCT in a transplantation-eligible patient with higher-risk MDS in the context of an anticipated prior treatment with AZA according to the AZA prognostic score.

<table>
<thead>
<tr>
<th>Variable/Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG</td>
<td>0-1</td>
<td>≥ 2</td>
<td></td>
</tr>
<tr>
<td>PB blasts</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>RBC units</td>
<td>&lt; 4 U/8 weeks</td>
<td>≥ 4 U/8 weeks</td>
<td></td>
</tr>
<tr>
<td>IPSS karyotype</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AZA prognostic score</th>
<th>0 = Low</th>
<th>1-3 = Intermediate</th>
<th>4-5 = High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS with AZA alone (months)</td>
<td>Not reached</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>2 years OS with AZA alone (estimated in %)</td>
<td>85</td>
<td>50</td>
<td>35</td>
</tr>
</tbody>
</table>

When to consider HCT in the context of AZA therapy?  
- No response to AZA or at disease progression  
- Try to deliver 6 cycles of AZA and then proceed to HCT  
- As early as possible during AZA therapy
Effect of Age on Transplant Outcome

<table>
<thead>
<tr>
<th>N</th>
<th>Age</th>
<th>regimen</th>
<th>NRM % at 4y</th>
<th>Relapse % 4y</th>
<th>OS % 4y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1333</td>
<td>56 (50-74)</td>
<td>RIC 62%</td>
<td>36</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>34%&gt;60</td>
<td>MA 38%</td>
<td>36 (50-60)</td>
<td>32 (50-60);p=0.2</td>
<td>34 (50-60)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td></td>
<td>39 (&gt;60)</td>
<td>41 (&gt;60);p=0.2</td>
<td>27 (&gt;60)</td>
</tr>
</tbody>
</table>

OS: advanced stage of disease at the time of transplantation

Lim et al: JCO 2010;28:405-411
Cumulative incidence of (A) nonrelapse mortality and (B) relapse in patients undergoing RIC or MA transplantation for acute myelogenous leukemia in first complete remission or for myelodysplastic syndrome.

McClune B L et al. JCO 2010;28:1878-1887
Kaplan-Meier estimates for disease-free survival (DFS) in (A) patients with acute AML in first complete remission and (B) patients with MDS.

McClune B L et al. JCO 2010;28:1878-1887
Factors Associated With Inferior Survival

• Advanced stage at disease
• Performance status
• Mismatched unrelated donors
• Unfavorable cytogenetics

Lim et al: JCO 2010;28:405-411
McClune: JCO 2010:28;1878-1887
Overall and Event-free Survival by Disease Status and Peripheral Blood Blasts

RIC Regimen

Is Cytoreduction Needed Prior to SCT

- Unfortunately there are no randomized trials

- Retrospective single center studies are inconclusive

- Intense induction regimen followed by 3 day rest followed by RIC with MR or MUD showed an OS at 2 years of 69% and 56%

Kroger Blood 2009;114:abstract 3387
Kaplan-Meier estimates of (A) 3-year overall survival, (B) 3-year event-free survival, (C) cumulative incidence of 3-year relapse, and (D) nonrelapse mortality (NRM) in 163 patients, according to the prior-to-transplantation treatment received.

©2012 by American Society of Clinical Oncology
Red Blood Cell Transfusion Dependence and Outcome after Allogeneic Peripheral Blood Stem Cell Transplantation in Patients with de Novo Myelodysplastic Syndrome

Uwe Platzbecker, Martin Bornhäuser, Ulrich Germing, Julian Stumpf, Bart L. Scott, Nicolaus Kröger, Rainer Schwerdtfeger, Alexandra Böhm, Guido Kobbe, Catrin Theuser, Werner Rabitsch, Peter Valent, Mohamed L. Sorror, Gerhard Ehninger and H. Joachim Deeg

Biology of Blood and Marrow Transplantation
Volume 14, Issue 11, Pages 1217-1225 (November 2008)
OS (A) and cumulative incidence of NRM (B) were dependent on pretransplantation ferritin level (A, $P = .03$; B, $P = .09$).
Cumulative incidence of NRM. Cumulative incidence with respect to LIC is given in A, whereas transfusion burden and ferritin are used as grouping variables in B and C.


©2012 by American Association for Cancer Research
Kaplan–Meier plot of the probability of OS with respect to LIC.

How we treat relapse after SCT

• Withdrawal of immunosuppression
• Donor lymphocyte infusion
• Chemotherapy
• Second SCT
• Hypomethylating agents (HMA)
• HMA and DLI
Hypomethylating agents for relapse after allogeneic stem cell transplant in patients with AML and high risk MDS

Thirteen patients with median age of 57 (22-62) and median time to relapse after SCT of 124 days (30-847)
Seven patients received MA and six RIC
Ten were treated with Decitabine and three with 5-Azacytidine, median cycle received 4 (1-9)
Nine patients achieved CR, three PR and one progressive disease
Eight patients achieved 100 donor chimerism
Six patients developed grade I-IV GVHD and three had isolated liver GVHD
Median survival: 308 (44-857) days, seven patients are alive and remain in remission.

Annie Im, A Raptis ASCO 2014
DLI Induced GVT is Tumor Specific

<table>
<thead>
<tr>
<th>Disease</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>15-36%</td>
</tr>
<tr>
<td>ALL</td>
<td>0-18%</td>
</tr>
<tr>
<td>MDS</td>
<td>25-40%</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>9-50%</td>
</tr>
<tr>
<td>NHL</td>
<td>20-60%</td>
</tr>
</tbody>
</table>

Porter D, ASH 2011
5-Azacytidine and DLI as Salvage Therapy

- 30 pt median age 56 (29-71)
- AML:28, MDS or MDS/MPD:2
- Up to 8 cycles Aza 100 mg/m2 dl-d5, median 3 courses were given
- DLI 1-5x10^6 to 1-5x10^8 every second Aza cycle, median DLI dose 5x10^6/Kg
- ORR:47%, CR:23%
- Median F/U 645 days 17% alive
- aGVHD: 37%, cGVHD: 17%

Schroeder T. Blood 2011;abstract 656
Maintenance

• 5-Azacytidine
• Lanalinomide
• Role of MRD
SUMMARY

• Allogeneic SCT is the only curative approach although randomized studies with no transplant modalities are needed
• Careful assessment of patients prior to considering SCT
• Timing of SCT and factors affecting outcome
• HMA in relapse
• Maintenance therapy post transplant with HMA and immunotherapy