Transplantation for MDS: Disease Risk, Age and Strategy:

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& University of Washington,
Seattle, WA

Patient Meeting May 20, 2017
“MDS” Spectrum
<table>
<thead>
<tr>
<th>Condition</th>
<th>CHIP</th>
<th>Non-clonal ICUS</th>
<th>CCUS</th>
<th>LR-MDS</th>
<th>HR-MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonality</td>
<td>+</td>
<td>−</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>−/+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>BM Blast %</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
<td>5-19%</td>
</tr>
<tr>
<td>Overall Risk</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Low (?)</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

CCUS = clonal cytopenias of undetermined significance; ICUS = idiopathic cytopenias of undetermined significance; CHIP = clonal hematopoiesis of indeterminate potential; LR = lower risk, HR = higher risk

Treat at all??

Transplant?
Classification(s)
<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Cytogenetic Abnormality</th>
<th>Survival (ms) Median (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single</td>
<td>Double</td>
</tr>
<tr>
<td>Very good</td>
<td>del(11q)</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>-Y</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>normal</td>
<td>incl.del(5q)</td>
</tr>
<tr>
<td></td>
<td>del(5q)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>del(12p)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>del(20q)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>del(7q), +8, i(17q), +19, any other</td>
<td>any other</td>
</tr>
<tr>
<td>Poor</td>
<td>der(3)(q21;q26), -7</td>
<td>incl. -7, del(7q)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very poor</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

J. Schanz et al, JCO, 2011
## IPSS-R Prognostic Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Cytogenetics</strong>*</td>
<td>Very Good</td>
</tr>
<tr>
<td>Marrow Blasts (%)</td>
<td>≤ 2</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥ 10</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 100</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>≥ 0.8</td>
</tr>
</tbody>
</table>

## IPSS-R Scores and Expected Survival (Years)

<table>
<thead>
<tr>
<th>Patient Age (ys)</th>
<th>Very Low (≤ 1.5)</th>
<th>Low (&gt; 1.5–3)</th>
<th>Intermediate (&gt;3 – 4.5)</th>
<th>High &gt;4.5 – 6</th>
<th>Very High (&gt;6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>8.8</td>
<td>5.3</td>
<td>3.0</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>≤ 60</td>
<td>NR</td>
<td>8.8</td>
<td>5.2</td>
<td>2.1</td>
<td>0.9</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>7.5</td>
<td>4.7</td>
<td>2.6</td>
<td>1.5</td>
<td>0.7</td>
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P.Greenberg et al, Blood 2012
Median Age at Diagnosis of MDS
70 - 75 Years:
Somatically-derived clones increase with age

Jaiswal et al, NEJM
Genovese et al NEJM

18.4% of 90-108 y/o
Patient Age and Mutations

-Log<sub>2</sub> P Value

Odds Ratio (log<sub>2</sub>)

Younger Age (<40 yr)  Older Age (≥40 yr)

Frequency in Total Cohort: • 1%  • 7%  • 14%  • 21%

- PIGA
- GATA2
- SBDS×2
- DNMT3A
- TET2
- SF3B1
- PPM1D
- SRSF2
- TP53

C. Lindsley et al NEJM, 2017
Do mutations matter?
Overall Survival by Mutation Number

17 genes sequenced in 1996 patients with OS data

ASXL1
CBL
DNMT3A
ETV6
EZH2
IDH1
IDH2
JAK2
KRAS
NPM1
NRAS
RUNX1
SRSF2
TET2
TP53
U2AF1

SF3B1

Number of Mutated Genes
- 0 (n=377)
- 1 (n=595)
- 2 (n=460)
- 3 (n=210)
- 4 (n=125)
- 5/6/7 (n=22)
- SF3B1 only (n=207)

R. Bejar et al – HoA 2015
MDS
Stage at Transplantation and Prognosis
## IPSS-R Prognostic Scores

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## IPSS-R Scores and Expected Survival (Years)

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<tr>
<th>Risk Category (Score)</th>
<th>Patient Age (ys)</th>
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<tr>
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<tr>
<td>≤ 60</td>
<td>NR</td>
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<tr>
<td>&gt; 60</td>
<td>7.5</td>
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P.Greenberg et al, Blood 2012
Transplant outcome by TRI

MDS transplantation risk index (TRI) calculation

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yr</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>IPSS-R</td>
<td>low intermediate high very high</td>
</tr>
<tr>
<td>Monosomal karyotype</td>
<td>no yes</td>
</tr>
<tr>
<td>HCT-CI</td>
<td>low/intermediate high</td>
</tr>
<tr>
<td>Refractoriness to induction chemotherapy</td>
<td>no yes</td>
</tr>
</tbody>
</table>

TRI is calculated as the sum of individual score values

Della Porta et al., Blood, 2014
Overall Survival, According to TP53 Mutation Status and Age

No TP53 mutation, <40 yr of age
No TP53 mutation, ≥40 yr of age
TP53 mutation, <40 yr of age
TP53 mutation, ≥40 yr of age

Years since Transplantation

Patients Who Survived (%)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>&lt;40 yr of age</th>
<th>≥40 yr of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>No TP53 mutation</td>
<td>214 159 133 115 100 78 42 23 13</td>
<td>1010 598 396 255 161 105 67 30 19</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>27 14 7 5 5 5 4 4 3</td>
<td>262 95 59 34 21 15 10 3 2</td>
</tr>
</tbody>
</table>

P<0.001
P=0.50

11%
20%

TP53, Age and Transplant Outcome

C. Lindsley et al NEJM 2017
Effect of non-transplant therapy on transplantation
Survival by salvage treatment in azacitidine treated patients

Th. Prébet et al. JCO 2011;29:3322-3327
Conditioning Intensity
Relapse/Progression by Disease and Treatment Arm

<table>
<thead>
<tr>
<th>Disease</th>
<th>MDS</th>
<th>AML</th>
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</thead>
<tbody>
<tr>
<td>HIC</td>
<td>3.7%</td>
<td>16.5%</td>
</tr>
<tr>
<td>RIC</td>
<td>37%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Incidence of Relapse

B. Scott et al, JCO, 2017
MRD and CONDITIONING Intensity
(Patients in *morphologic remission*)

**CYTO NEG**

- Low Intensity
- High Intensity

**CYTO POS**

- Low Intensity
- High Intensity

- Typically used in older patients

**Survival**

- **P** = 0.65

- **P** < 0.0001

**Relapse**

- M. Festuccia et al, BBMT 2016
Flu/Treo/TBI Treatment Scheme

TBI 2 Gy

HCT

FLU 30 mg/m²/day

TREO 14 g/m²/day

Days -6, -5, -4, -3, -2, -1, 0, +1, +3, +6, +11, +56, +180

Methotrexate 10 mg/m²/dose

Tacrolimus BID

Gyurkocza et al, BBMT 2014
Impact of Cytogenetics in MDS (n=36)

Relapse Survival

Good/Interm (n=20) – 27%
P = 0.31

Good/Interm (n=20) – 82%

Poor (n=16) – 13%
P = 0.45

Poor (n=16) – 68%

Gyurkocza et al, BBMT, 2014
Does age affect the outcome of transplantation?
Low Intensity Conditioning:
Outcome by Age (Various Diagnoses)

NRM

Survival

M. Sorror et al, JAMA, 2011
Comorbidities, Age and Survival

Sorror et al, J Clin Onc 2014
Overall Survival

5-AZA versus HCT

Donor vs No Donor

U.Platzbecker et al, BBMT, 2012

Robin et al, ASH 2013 #301
RIC in patients 60 – 70 ys of age

Two ongoing prospective trials

1. German Prospective Vidaza Trial
   (Kröger/Platzbecker)
   - N = 254, newly diagnosed MDS
   - Age 55-70 ys, Int-2 / High or Int-1 (“bad” genes)
   - Aza → Donor vs. No donor assignment

2. BMT CTN 1102 (Nakamura / Cutler)
   - N = Up to 400 MDS
   - Age > 50 ys, Int-2 / High IPSS
   - Donor RIC vs. No donor (Best Supportive Care)
   - QOL and Cost Effectiveness analyses
And the “cost”?
HCT-CI and acute GVHD grades III-IV

![Graph showing the probability of grades 3-4 GVHD over days after HCT for different HCT-CI categories.](image)

- HCT-CI 5+ (n=316)
- HCT-CI 1-2 (n=930)
- HCT-CI 3-4 (n=786)
- HCT-CI 0 (n=953)
GVHD and Age

• Chronic GVHD increases with age
• Because of age → reduced intensity conditioning (RIC)
• To assure engraftment with RIC → PBPC
• PBPC → more chronic GVHD
• Steroids as frontline therapy
• Steroids poorly tolerated in older individuals
Chronic GVHD and QOL

Months

A couple of years
Summary

• MDS is curable by hematopoietic cell transplantation (HCT), even in “fit” patients in their ‘70s.
• However, outcome “early” after HCT is not superior to outcome with hypomethylating therapy
• Age-associated mutations may affect the pathophysiology of the disease
• GVHD prevention is a major challenge
Thank you

• All colleagues
• Nurses and support staff
• .......and all our patients