The Emerging Role of Allogeneic Transplantation in Older MDS Patients

Wael Saber, MD, MS
Outline

- Overview of recent trends and outcomes of allogeneic transplantation for older MDS adults in the US

- Is age an important predictor of post-HCT outcomes among those who are older than 40?

- Compared to non-transplant therapies, what is the optimal role of HCT in caring for older MDS patients?
Myelodysplasia (MDS)

- Clonal, Pre-Leukemic diseases
- Variable progression over time
  - Staging per IPSS, WPSS and IPSS-R Scoring Systems
- New molecular prognostic features

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
<th>Prognosis/Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUNX1</td>
<td>20%</td>
<td>poor prognosis</td>
</tr>
<tr>
<td>MDS-EV1</td>
<td>n/a</td>
<td>~5% cases over-expressed</td>
</tr>
<tr>
<td>TP53</td>
<td>10%</td>
<td>poor prognosis, therapy related MDS</td>
</tr>
<tr>
<td>RAS</td>
<td>15%</td>
<td>potential treatment targets in downstream pathway members</td>
</tr>
<tr>
<td>JAK2</td>
<td>5%</td>
<td>most often seen in RARS-T, potential treatment with JAK2 inhibitors</td>
</tr>
<tr>
<td>TET2</td>
<td>12-26%</td>
<td>seen in various myeloid malignancies, potential link to DNA methylation and treatment with hypomethylating agents</td>
</tr>
<tr>
<td>ASXL-1</td>
<td>11-18%</td>
<td>potential treatment targets in histone modifying enzymes and ATRA</td>
</tr>
<tr>
<td>EZH2</td>
<td>6%</td>
<td>seen in various myeloid and solid tumor malignancies, potential treatment targets in histone modifying enzyme</td>
</tr>
</tbody>
</table>

Greenberg et al, Blood 2012; Slide Courtesy C. Cutler
Therapy for MDS – DNA Hypomethylation

Figure 3  Overall survival

Pierre Fenaux, Ghulam J Mufti, Eva Hellstrom-Lindberg, Valeria Santini, Carlo Finelli, Aristoteles Giagounidi...

Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study

http://dx.doi.org/10.1016/S1470-2045(09)70003-8
Adjusted Probability of Overall Survival for MDS

Overall P-value = 0.005 (2 df)
8/8 MUD vs. MRD = 1.24 (0.98-1.56)
7/8 MUD vs. MRD = 1.62 (1.21-2.17)
7/8 MUD vs. 8/8 MUD = 1.30 (1.01-1.68)

Saber et al. ASH 2012
Most Common Indications for Allogeneic HSCT in Recipients ≥ 40 Years of Age, US Centers only 2000-2010

<table>
<thead>
<tr>
<th>Age Group</th>
<th>AML</th>
<th>NHL</th>
<th>MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-50yrs</td>
<td>62%</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>50-60yrs</td>
<td>68%</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>&gt;60yrs</td>
<td></td>
<td>75%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Proportion of Allogeneic HSCT Performed for MDS, in Recipients ≥ 40 Years of Age
US Centers only 2000-2011

- Myleoablative, HLA-matched Sibling Donor
- Myleoablative, Unrelated Donor
- Non-myleoablative, HLA-matched Sibling Donor
- Non-myleoablative, Unrelated Donor

Transplants, %

- 8% for 40-50yrs
- 13% for 50-60yrs
- 16% for >60yrs
Increasing access to HCT for MDS in patients ≥ 65 years old
Proportion of Allogeneic HSCT Performed for MDS, in Recipients $\geq$ 40 Years of Age
US Centers only 2000-2011

- Myleoablative, HLA-matched Sibling Donor
- Myleoablative, Unrelated Donor
- Non-myleoablative, HLA-matched Sibling Donor
- Non-myleoablative, Unrelated Donor

Transplants, %

2000-2003: 11.1%
2004-2007: 11.6%
2008-2011: 13.4%
Allogeneic Stem Cell Sources for MDS in Recipients ≥ 40 Years of Age, US Centers Only 2000-2011

- Bone Marrow
- Peripheral Blood
- Cord Blood

Transplants, %

- 2000-2003
- 2004-2007
- 2008-2011
One-year survival after transplants for MDS
US Centers Only, 2000-2010

One-Year Survival, %

- Myleoablative, HLA-matched Sibling Donor
- Myleoablative, Unrelated Donor
- Non-myleoablative, HLA-matched Sibling Donor
- Non-myleoablative, Unrelated Donor
One-year survival after HLA-matched sibling transplants for MDS
US Centers Only, 2000-2010

One-Year Survival, %

0 20 40 60 80 100

'00 '01 '02 '03 '04 '05 '06 '07 '08 '09 '10

40-50yrs
50-60yrs
>60yrs

CIBMTR
One-year survival after unrelated donor transplants for MDS
US Centers Only, 2000-2010

One-Year Survival, %

- 40-50yrs
- 50-60yrs
- >60yrs

[Graph showing survival rates across different age groups from 2000 to 2010]
Causes of death after allogeneic transplants performed for MDS, 2008-2010 - US centers only -

Recipients age 40- 50 years

- Primary Disease (29%)
- GVHD (20%)
- Infection (23%)
- Unknown (9%)
- Organ Failure (13%)
- Hemorrhage (3%)

New Malignancy (3%)

Recipients age 50- 60 years

- Primary Disease (43%)
- GVHD (16%)
- Infection (17%)
- Unknown (8%)
- Organ Failure (11%)

New Malignancy (3%)

Recipients age 60+ years

- Primary Disease (38%)
- GVHD (24%)
- Infection (15%)
- Unknown (6%)
- Hemorrhage (1%)
- Organ Failure (15%)

New Malignancy (3%)

Unknown (9%)

Hemorrhage (2%)

Known (1%)
Please choose the correct statement

A. Allogeneic HCTs are rarely performed in older MDS patients

B. Bone marrow is the most common graft source for allogeneic HCT for older MDS patients

C. Unrelated donors currently represent the most frequent donor source for HCT in older MDS patients
Overview of recent trends and outcomes of allogeneic transplantation for older MDS adults in the US

Is age an important predictor of post-HCT outcomes among those who are older than 40?

Compared to non-transplant therapies, what is the optimal role of HCT in caring for older MDS patients?
NRM and Relapse of 545 patients 40+ y.o. receiving RIC allo HCT for AML in CR1/MDS, 1995-2005, by age

Fig 1. Cumulative incidence of (A) nonrelapse mortality (P = .66) and (B) relapse (P = .87) in patients undergoing reduced-intensity conditioning or nonmyeloablative transplantation for acute myelogenous leukemia in first complete remission or for myelodysplastic syndrome.

McClune B et al. JCO 2010;28:1878-1887
Fig 2. Kaplan-Meier estimates for disease-free survival (DFS) in (A) patients with acute myelogenous leukemia (AML) in first complete remission (CR1) and (B) patients with myelodysplastic syndrome (MDS). Kaplan-Meier estimates for overall survival (OS) in (C) patients with AML in CR1 and (D) patients with MDS. Multivariate analysis for DFS ($P = .81$) and OS ($P = .74$) is shown in Table 5.
Outline

- Overview of recent trends and outcomes of allogeneic transplantation for older MDS adults in the US

- Is age an important predictor of post-HCT outcomes among those who are older than 40?

- Compared to non-transplant therapies, what is the optimal role of HCT in caring for older MDS patients?
Optimizing Timing of Transplantation

Cutler et al, Blood 2004
RIC Decision Analysis Results

<table>
<thead>
<tr>
<th>Variables</th>
<th>Early RIC HCT</th>
<th>Delayed RIC HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low/intermediate-1 IPSS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall life expectancy (months)</td>
<td>38</td>
<td>77</td>
</tr>
<tr>
<td>QALE: transfusion independent (months)</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>QALE: transfusion dependent (months)</td>
<td>35</td>
<td>46</td>
</tr>
<tr>
<td><strong>Intermediate-2/high IPSS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall life expectancy (months)</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>QALE: Higher-risk MDS morbidity (months)</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>QALE: GVHD morbidity (months)</td>
<td>22</td>
<td>15</td>
</tr>
</tbody>
</table>
Coverage with Evidence Development

CMS issued decision Aug 2010 allowing “coverage with evidence development (CED)”

- Suggests insufficient evidence
  - “...evidence does not demonstrate that the use of HCT improves health outcomes in Medicare beneficiaries with MDS.”
  - “paucity of evidence regarding the use of HCT in patients with MDS who are 65 years or older”
- Will cover costs of HCT if patients enrolled in a study that will provide CMS with data (“evidence”) to determine the value of the procedure in the Medicare population
The Outcome of Hematopoietic Cell Transplantation (HCT) for Myelodysplastic syndrome (MDS): First Report of the Coverage with Evidence Development (CED) in Medicare Beneficiaries > 65 years

Atallah et al. ASH 2012
Increasing access to HCT for MDS in patients ≥ 65 years old

![Bar chart showing the number of transplants per year from 2009 to 2012. The chart includes the number of transplants through September 2012 and the estimated additional transplants through the end of 2012. The numbers are as follows:

- 2009: 73
- 2010: 78
- 2011: 149
- 2012: 187 (includes 37 estimated additional transplants through the end of 2012)]
Current CIBMTR CED Observational Study

- Primary outcome: Early (100-day) mortality of HCT recipients 65 and older

  - Hypothesis: 100-day mortality rate in recipients 65 and older is ≤20%

- 240 patients with three planned interim analyses

- In May 2012, first 120 patients completed at least 100 days of follow up
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>120</td>
</tr>
<tr>
<td>Centers, n</td>
<td>58</td>
</tr>
<tr>
<td><strong>Patient-related</strong></td>
<td></td>
</tr>
<tr>
<td>Recipient Age, median (range)</td>
<td>67 (65-74) y</td>
</tr>
<tr>
<td>KPS $\geq 90$</td>
<td>60%</td>
</tr>
<tr>
<td>Sorror comorbidity score $\geq 3$</td>
<td>45%</td>
</tr>
<tr>
<td><strong>Disease-related</strong></td>
<td></td>
</tr>
<tr>
<td>Therapy-related MDS</td>
<td>20%</td>
</tr>
<tr>
<td>Int2/high IPSS prior to HCT</td>
<td>30%/5%</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>120</td>
</tr>
<tr>
<td>Transplant-related</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood stem cells</td>
<td>90%</td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
</tr>
<tr>
<td>8/8 MUD</td>
<td>60%</td>
</tr>
<tr>
<td>HLA-Identical sibling</td>
<td>25%</td>
</tr>
<tr>
<td>Nonmyeloablative/RIC conditioning</td>
<td>75%</td>
</tr>
<tr>
<td>GVHD prophylaxis</td>
<td></td>
</tr>
<tr>
<td>FK-based</td>
<td>60%</td>
</tr>
<tr>
<td>CSA-based</td>
<td>20%</td>
</tr>
<tr>
<td>ex vivo T-cell depletion</td>
<td>5%</td>
</tr>
<tr>
<td>In vivo T-cell depletion</td>
<td>30%</td>
</tr>
</tbody>
</table>
## Causes of Death in first 100 days in patients 65 and older

<table>
<thead>
<tr>
<th>Variable</th>
<th>25 (21%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of deaths in first 100 days*</td>
<td>25 (21%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ failure</td>
<td>30%</td>
</tr>
<tr>
<td>Relapse</td>
<td>25%</td>
</tr>
<tr>
<td>Infection</td>
<td>20%</td>
</tr>
<tr>
<td>GVHD</td>
<td>10%</td>
</tr>
<tr>
<td>Graft failure</td>
<td>5%</td>
</tr>
<tr>
<td>IPn</td>
<td>5%</td>
</tr>
</tbody>
</table>

* 33 or more deaths (28%) needed to occur to surpass the stopping rules
A Multi-Center Phase III Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients Age 50 or Older with Intermediate-2 and High Risk Myelodysplastic Syndrome

BMT CTN 1102

Ryotaro Nakamura, MD
Corey Cutler, MD MPH

January 2013
Study Objectives

Primary Objective

- Compare the three-year overall survival probability between the two study arms using an intent-to-treat analysis
  - Arm 1: RIC alloHCT
  - Arm 2: Non-Transplant Therapy / Best Supportive Care

Secondary Objectives

- Compare leukemia-free survival (LFS) at 3 years from enrollment
- Compare QOL measures between treatment arms
Basic Design

- Donor vs. No Donor Comparison of Patients Referred for Transplantation
  - “Does Transplant Help”
- Intention to Treat
- No mandate of transplant or non-transplant regimen
Eligibility

- De novo MDS with CURRENT or PRIOR Intermediate-2 / High-risk IPSS Score
- Aged 50-75 years
- Marrow (30 days) with < 20% blasts
- Any therapy prior to registration
- KPS > 70 / ECOG ≤ 1
- NO specific lab testing eligibility
  - Available tests + gestalt at transplantation consultation
- No formal MUD search activated.
  - Sibling donor search or with a known MRD or no MRD donor is allowed
- Treatment Compliance Planned
  - Intent to proceed to RIC transplantation if a donor is found
  - No intent to pursue alternative donor transplantation at the time of enrollment
Exclusion

- Secondary/therapy-related MDS
- Acute Myelogenous Leukemia (current / prior)
- Prior Autologous / Allogeneic HCT
- Uncontrolled bacterial, viral (incl HIV) or fungal infection
- Concurrent malignancy
Design

Donor Arm

Screening/Study Enrollment

Donor Search (3 months)

Donor

HCT

Routine 3 month follow-up

Standard CIBMTR Follow-up

No-Donor Arm

QOL baseline

No-HCT candidate

QOL 6 mos

QOL 12 mos

QOL 18 mos

QOL 24 mos

QOL 36 mos

Follow-up for Survival, AML progression, and QOL – 3 yrs*

Routine 3 month follow-up

Alternative Donor

HCT

Standard CIBMTR follow-up

CIBMTR
Design – Treatment Assignment

♦ Once Enrolled - 90 days maximum to Donor/No Donor assignment

♦ Based on likelihood of identifying donor after 90 days – NMDP data

♦ Analysis as NO DONOR for events occurring prior to assignment

♦ Balances bias with those who arrive with known donors and suffer early events

♦ Intention to treat, even if:
  • Declines transplant with known donor
  • Undergoes alternative donor transplant (no donor arm)
Statistics – Assumptions

- CIBMTR 3 year OS for RIC Transplantation

<table>
<thead>
<tr>
<th>Group</th>
<th>Prob (95% CI)</th>
<th>2011 CIBMTR Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>38 (27 – 50)%</td>
<td>265 (age 50-65)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>33 (16 – 54)%</td>
<td>152 (age &gt; 65)</td>
</tr>
<tr>
<td>Combined</td>
<td>37 (27 – 47)%</td>
<td>n = 417</td>
</tr>
</tbody>
</table>

- Baseline Data – Azacytidine
- Compassionate use program n = 282, (Itzykson et al, Blood 2011)
- 3 year OS = 20-25%
## Power to Detect 15% Increase in OS Probability in the Transplant Arm for Various Survival Probabilities and Proportions of Donor Availability

<table>
<thead>
<tr>
<th>Donor Availability</th>
<th>Total Sample size (HCT, Non-HCT)</th>
<th>Three-year OS</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HCT</td>
<td>Non-HCT</td>
</tr>
<tr>
<td>60%</td>
<td>338 (203, 135)</td>
<td>35%</td>
<td>20%</td>
</tr>
<tr>
<td>70%</td>
<td>400 (280, 120)</td>
<td>35%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40%</td>
<td>25%</td>
</tr>
</tbody>
</table>
Protocol Timeline

❖ PRC Review / Approval Jan 2013
   ♦ Consent and FAQ documents included
❖ Needs Biomarker and Toxicity Committee Reviews
❖ Steps:
   ♦ Steering Committee Approval
   ♦ Release to IRBs
   ♦ Forms and Logistics being worked on now
❖ Goal:
   ♦ Accrual before Q4 2013
Please choose the correct statement

1. Based on a CIBMTR study, MDS patients aged 55 or older have higher risk of mortality after allogeneic HCT compared to MDS patients aged 40-54

2. A 67 yo man with IPSS Intermediate-2 Risk MDS should undergo allogeneic HCT immediately

3. A 67 yo man with IPSS Intermediate-1 Risk MDS should undergo allogeneic HCT immediately