MDS – The role of haploidentical allogeneic SCT: results and for whom do I consider?

Fábio Kerbauy
July/2018
• No major health issues, anemia and pulmonary infection in july/2018
• L: 800 (400n); Hb: 9.0; PLQ: 30.000

**Bone marrow:** 18% blast, dysplastic features 3 series

**IFT:** 16.2% progenitor cells: CD34+ and CD13, CD33, CD38, CD71, CD105, CD117, HLA DR e MPO

**Kt:** 44,XX,+der(6)t(3;6)(p21;q25),-7,der(7)t(1;7)(p22;p22),der(10)t(5;10)(q22;q11.2),-17,-18,add(19) (p13)[6]/46,XX[14]

**FISH:** deleção do gene TP53

**MDS – AREB-II Very High Risk**
Revised-IPSS

NCCN - 2017 – Low Risk

IPSS: Low/Intermediate-1
IPSS-R: Very Low, Low, Intermediate
WPSS: Very Low, Low, Intermediate

Clinically significant cytopenia(s) or increased marrow blasts → Supportive care as an adjunct to treatment

Symptomatic anemia →
- Clinically relevant thrombocytopenia or neutropenia or increased marrow blasts
- Azacitidine or Decitabine or Immunosuppressive therapy (IST) for select patients or Clinical trial

No del(5q) ± other cytogenetic abnormalities →
- Serum EPO ≤500 mU/mL → See MDS-4
- Serum EPO >500 mU/mL → See MDS-4

del(5q) ± one other cytogenetic abnormality → See MDS-4

Disease progression/No response → Clinical trial or Consider allo-HCT for select patients

Notes:
- $^a$ Consider an MDS-4 session
- $^b$ Consider an MDS-4 session
- $^c$ Consider an MDS-4 session
- $^d$ Consider an MDS-4 session
- $^e$ Consider an MDS-4 session
- $^f$ Consider an MDS-4 session
- $^g$ Consider an MDS-4 session
- $^h$ Consider an MDS-4 session
- $^i$ Consider an MDS-4 session
- $^j$ Consider an MDS-4 session
- $^k$ Consider an MDS-4 session
- $^l$ Consider an MDS-4 session
- $^m$ Consider an MDS-4 session
- $^n$ Consider an MDS-4 session
- $^o$ Consider an MDS-4 session
- $^p$ Consider an MDS-4 session
- $^q$ Consider an MDS-4 session
- $^r$ Consider an MDS-4 session
- $^s$ Consider an MDS-4 session
- $^t$ Consider an MDS-4 session
- $^u$ Consider an MDS-4 session

Clinical trial or Consider allo-HCT for select patients
NCCN- 2017 – High/Int Risk

IPSS: Intermediate-2, High
IPSS-R: Intermediate, High, Very High
WPSS: High, Very High

Donor stem cell source available:
  Yes → Allo-HCT\textsuperscript{cc} or Azacitidine followed by HCT\textsuperscript{bb,cc} or Decitabine followed by HCT\textsuperscript{bb,cc} or High-intensity chemotherapy\textsuperscript{ee} followed by HCT\textsuperscript{bb,cc}

  No → Azacitidine (preferred) (category 1)\textsuperscript{dd} or Decitabine\textsuperscript{dd} or Clinical trial

Relapse after HCT or No response\textsuperscript{t}

Consider HCT or donor lymphocyte infusion (DLI)\textsuperscript{ff} or Azacitidine\textsuperscript{dd} or Decitabine\textsuperscript{dd} or Clinical trial

Response\textsuperscript{t} → Continue

No response\textsuperscript{t} or relapse

Clinical trial or Supportive care\textsuperscript{r}
Current treatment algorithm - 2018

Fig. 1 MDS treatment algorithm as described in the text. Clinical trials should be considered for all patients, but it is recognized that many patients will not have access to trials or will not be eligible for available trials or will not want to go on trials, especially those requiring travel to a major center. In fact only a very small proportion of patients with MDS are currently enrolled on prospective interventional trials. However, increased trial enrollment is an important goal given the continued poor outcomes with MDS. EPO erythropoietin, ESA erythropoiesis-stimulating agent, HMA DNA hypomethylating agent, IST immunosuppressive therapy (anti-thymocyte globulin, cyclosporine, or tacrolimus).
High Risk MDS – Phase III 5-Aza

OS benefit: + 9.5 mos

Time to AML: 17.8 vs. 11.5 mos

Fenaux P. et al. Leukemia 2009
Donor x No Donor – High risk MDS

Robin M et al, Leukemia, 2015
HCT for SMD – CIBMTR

![Bar graph showing the number of transplants by year and age group from 2000 to 2014. The age groups are 20-40 years, 41-50 years, 51-64 years, and 65+ years. The number of transplants decreases from 2000 to 2014.]
Allo HCT in 70+ yo patients – USA
Median age: 72 (70-84)
Impact of drug development on SCT

EBMT activity survey. Passweg et al. BMT, 2017; 52: 191-196
Indications for Hematopoietic Cell Transplant in the US, 2016

- Allogeneic (Total N=8,519)
- Autologous (Total N=14,181)

Number of Transplants

- Myeloma / PCD
- NHL
- AML
- MDS / MPN
- ALL
- HD
- Other Cancer
- Other Non-Malignant
- Aplastic Anemia
- CML
- CLL

CIBMTR
Center for International Blood & Marrow Transplant Research
Case study– SMDS, 55a

Possible donors (by august/2018 – 2 months from diagnosis)

• 4 sons – haploidentical
• Brazilian donor registry – REDOME (1 international donor available)

While waiting

• 5-AZA as a bridge to HCT

QUESTION: MUD x haplo?
MA (Bu$^T$Cy) in MDS – Median 46yo

TRM 100d e 1 y
MRD=12% / 28%
MUD = 13% / 30%

Deeg et al, Blood 2002; 100:1201-1207
MRD x MUD in MDS patients - CIBMTR


Robin M et al. BMT, 2013; 1-6
Post HCT Cy for haplo – Johns Hopkins
Post HCT Cy for haplo – Johns Hopkins

- **BMT Day**: -6
- **Fludarabine 30 mg/m²/day**: -5
- **Cy 14.5 mg/kg/day**: -4
- **-3**: TBI 200 cGy
- **-2**: Bone Marrow Infusion
- **Day 0**: G-CSF 5 µg/kg/d
- **MMF 15 mg/kg po tid**: 5
- **Tacrolimus**: 5 to 180
- **Cy 50 mg/kg/day**

Brodsky RA et al. BMT; 42: 523-527, 2008
Post HCT Cy for haplo – OS (n=210)

- ALL (n=16)
- AML (n=43)
- MDS, MPD (n=25)

- CLL (n=24)
- HL (n=30)
- NHL (n=66)
Type of donor for MDS patients

MRD = MUD

X

Haploidentical (Post transplant Cyclophosphamide)

ASH - 2016

Transplantation for myelodysplastic syndromes: who, when, and which conditioning regimens

Wael Saber and Mary M. Horowitz

Only a handful of HCTs from haploidentical donors for patients with MDS have been performed to date, and very few were performed using the novel platform of posttransplant cyclophosphamide.

HLA- identical siblings and 8/8 matched unrelated donors be considered standard therapy for MDS
### AML/MDS - Haplo x MRD x MUD

Haplo (n=32)

<table>
<thead>
<tr>
<th>Measure</th>
<th>All Patients (N = 227)</th>
<th>By Donor Type</th>
<th>MRD (n = 87)</th>
<th>MUD (n = 108)</th>
<th>Haplo (n = 32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at HSCT, median (range), yr</td>
<td>60 (20-76)</td>
<td>60 (24-76)</td>
<td>62 (21-76)</td>
<td>52 (20-67)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>128 (56)</td>
<td>52 (60)</td>
<td>60 (56)</td>
<td>16 (50)</td>
<td>.610</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>99 (44)</td>
<td>35 (40)</td>
<td>48 (44)</td>
<td>16 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCT-CI total scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (0-12)</td>
<td>3 (0-12)</td>
<td>3 (0-9)</td>
<td>1.5 (0-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPC, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>143 (63)</td>
<td>84 (97)</td>
<td>58 (54)</td>
<td>1 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>84 (37)</td>
<td>3 (3)</td>
<td>50 (46)</td>
<td>31 (97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.994</td>
</tr>
<tr>
<td>AML, MDS/AML</td>
<td>151 (67)</td>
<td>58 (67)</td>
<td>71 (66)</td>
<td>22 (69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS</td>
<td>33 (15)</td>
<td>12 (14)</td>
<td>17 (16)</td>
<td>4 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>43 (19)</td>
<td>17 (20)</td>
<td>20 (19)</td>
<td>6 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>70 (31)</td>
<td>25 (29)</td>
<td>26 (24)</td>
<td>19 (59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CR</td>
<td>157 (69)</td>
<td>62 (71)</td>
<td>82 (76)</td>
<td>13 (41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetic risk, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.663</td>
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<tr>
<td>n</td>
<td>220</td>
<td>83</td>
<td>106</td>
<td>31</td>
<td></td>
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</tr>
<tr>
<td>Good</td>
<td>22 (10)</td>
<td>7 (8)</td>
<td>11 (10)</td>
<td>4 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>110 (50)</td>
<td>38 (46)</td>
<td>55 (52)</td>
<td>17 (55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>88 (40)</td>
<td>38 (46)</td>
<td>40 (38)</td>
<td>10 (32)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HCT-CI indicates hematopoietic cell transplantation comorbidity index; HPC, hematopoietic progenitor cells; CR, complete remission.

* Kruskal-Wallis test.
† Fisher’s exact test.
AML/MDS - Haplo x MRD x MUD

Haplo (n=32)

Haplo HCT for MDS – EBMT 2017
(n=228)

Selecting the best haplo donor

- PRA (anti-HLA)
- ABO/Rh
- CMV status
Case study—SMDS, 55ª PRA+ (DSA+)

<table>
<thead>
<tr>
<th>Resultados</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Especificidade</strong></td>
</tr>
<tr>
<td>NC</td>
</tr>
<tr>
<td>PC</td>
</tr>
<tr>
<td>B76</td>
</tr>
<tr>
<td>A80</td>
</tr>
<tr>
<td>A24</td>
</tr>
<tr>
<td>A1</td>
</tr>
<tr>
<td>A24</td>
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<tr>
<td>A23</td>
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<tr>
<td>A32</td>
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<tr>
<td>A25</td>
</tr>
<tr>
<td>B44</td>
</tr>
<tr>
<td>B45</td>
</tr>
<tr>
<td>B44</td>
</tr>
<tr>
<td>B82</td>
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<tr>
<td>B57</td>
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<tr>
<td>B57</td>
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<tr>
<td>B58</td>
</tr>
<tr>
<td>B63</td>
</tr>
<tr>
<td>A43</td>
</tr>
<tr>
<td>A26</td>
</tr>
</tbody>
</table>

**REATIVIDADE CONTRA PAINELES (PRA)**

<table>
<thead>
<tr>
<th><strong>PRA LUMINEX (IgG)</strong></th>
<th><strong>SORO DE 10.09.18</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QUALITATIVO</strong></td>
<td><strong>CLASSE I</strong></td>
</tr>
<tr>
<td>POSITIVO</td>
<td>NEGATIVO</td>
</tr>
</tbody>
</table>

**PRA LUMINEX (IgG) Single Antigen**

<table>
<thead>
<tr>
<th><strong>SORO DE 10.09.18 - MFI ≥ 1500</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESPECIFICIDADES DOS Acs ANTI HLA DETECTADOS</strong></td>
</tr>
</tbody>
</table>

**MFI: MEAN FLUORESCENCE INTENSITY**

<table>
<thead>
<tr>
<th><strong>CLASSE I (HLA A,B)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRA calculado</strong></td>
</tr>
</tbody>
</table>

*O cálculo do PRA baseia-se na frequência de especificidades HLA A,B,DR em amostra de 4000 doadores falecidos de rim da regional I do estado de São Paulo, considerando especificidades detectadas no soro do receptor com MFI ≥ 1500.*
Disensitizatin for DSA+

[Diagram showing treatment schedule with labels for Bortezomib, PE, IVIG, Rituximab, Melphalan 140 mg/m², Fludarabine 40 mg/m², TBI, Buffy coat, and Stem cell infusion]
By December/2018 – 5 months from diagnosis

• 4 cycles of 5-Aza: Less transfusion dependence
• BM: 20% blasts

• 1 son – haploidentical ABO/CMV matched (DSA+)
• 1 MUD 10/10

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A imunogenicidade preditiva da compatibilidade DPB1 para este par é: Permissivo
Case study– SMDS, 55a

TODAY: D+60 post HCT

• Low HCT-CI
• MUD (PBSC 6 x 10e6 CD34+/kg)
• Bu (6000 AUC) + Fludarabine / FK/MTX/ATG
• Complications: Mucositis grade IV/neutropenic fever
• Engraftment: D+12
• GVHD skin grade 2 resolved
• 100% chimerism/ MRD-
MDS and mutations
HCT in TP53 mutations AML/MDS
Impact of HCT-CR

Ciurea SO et al. Blood, 2018
Haplo for MDS
For whom I consider

• Standard of care: MRD or MUD

• Haplo as alternative
  - High-risk/very high-risk patients
  - Fit patients (HCT-CI score)
  - Choose the best donor (ABO/CMV/PRA)
  - MA x NMA
Haplo for MDS
For whom I consider

ALWAYS DISCUSS CASE BY CASE

- Specific risk scores
- Pre HCT therapy
- Conditioning regimen intensity
- Post HCT maintenance
obrigado!

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