ALLOGENEIC HCT FOR MYELOFIBROSIS

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Hematopoietic Cell Transplants (HCT)

• Allogeneic (HLA Matching)
  – sibling donor (8/8)
  – matched related (MRD) (7/8)
  – matched unrelated (MUD, URD) (10/10, 9/10)
  – Cord blood (4-6/6) (Double cords for adults)
  – Haploidentical donor (5/10)
Source of Cells

- Bone marrow
- G-CSF Primed mobilized PBSC
- Umbilical cord blood
Annual Number of HCT Recipients in the US by Transplant Type

- Adjusted Autologous HCT
- Adjusted Allogeneic HCT

Number of Transplants


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Allogeneic HCT Recipients in the US, by Donor Type

- URD-BM / PB
- HLA-identical Sib
- Other Relative
- URD / UCB

Graph showing the number of transplants from 1980 to 2016.
Trends in Allogeneic HCT in the US by Recipient Age

Number of Transplants

<60 Years | 60-69 Years | ≥70 Years


^Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma
Indications for Hematopoietic Cell Transplant in the US, 2017

- **Allogeneic** (Total N=8,780)
- **Autologous** (Total N=14,599)

Number of Transplants

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

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### Time Trends in HCT for MF: CIBMTR Data

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>72</td>
<td>213</td>
<td>336</td>
</tr>
<tr>
<td>Age Groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>25 (35%)</td>
<td>82 (38%)</td>
<td>151 (45%)</td>
</tr>
<tr>
<td></td>
<td>4 (6%)</td>
<td>25 (12%)</td>
<td>87 (26%)</td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced Intensity Conditioning</td>
<td>15%</td>
<td>37%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Adopted from: Gupta et al. (Blood-2012)
Annual number of HCTs in patients 70 years and older by indication.

Lori Muffly et al. Blood 2017;130:1156-1164
CIBMTR reporting trends showing transplant activity in myelofibrosis.


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COH - NUMBER OF TRANSPLANTS FOR MYELOFIBROSIS
Therapeutic Benefits of Hematopoietic Cell Transplants

CURATIVE INTENT

1. Preparative regimens - myeloablative vs RIC
2. Post transplant alloreactivity
   - Graft vs. MPN effect
Complications

- Acute and chronic GVHD
- Delayed engraftment; graft failure; relapse
- Infections - CMV, zoster, fungus, bacteria
- SOS (VOD); TMA; DAH
- Avascular necrosis
- Cataracts
- Infertility
- Secondary malignancies (sq. cell Ca)
- Cognitive deficits
Causes of Death after Unrelated Donor HCT done in 2015-2016

Died within 100 days post-transplant

- 24% Primary Disease
- 20% Infection
- 18% Organ Failure
- 11% Hemorrhage
- 10% GVHD
- 12% Graft Rejection
- 2% Second Malignancy
- 3% Other
- 1% Other

Died at or beyond 100 days post-transplant*

- 48% Primary Disease
- 13% Infection
- 13% GVHD
- 12% Organ Failure
- 10% Second Malignancy
- 1% Graft Rejection
- 1% Other

*Data reflects 3-year mortality
2016 CED Decision: HCT in Myeloma, Sickle Cell Disease, Myelofibrosis

- In 2015, NMDP, ASBMT, CIBMTR requested coverage expansion for Myelofibrosis, SCD and Lymphoma

- In January 2016, CMS expanded coverage for alloHCT to some beneficiaries with Multiple Myeloma, Sickle Cell Disease & Myelofibrosis under Coverage with Evidence Development (CED)
  - Reimbursement provided only if the patient is enrolled in a **CMS-approved clinical trial** designed to evaluate benefit in the Medicare population
  - Similar to the current CED for MDS
Allo HCT Coverage for Medicare Patients with Myelofibrosis at COH
Indications for HCT for MPN

- Primary Myelofibrosis DIPSS Int -2 or High risk
- Secondary MF after ET or PV
- AML after MF
- ELN: < 5 yr expected survival; frequent transfusion requirement
DIPSS for Predicting Survival IN PMF

- Adverse prognostic Factors:
  - Age > 65
  - *Hb < 10 g/dl
  - WBC > 25 K/uL
  - PB blasts ≥1%
  - Constitutional symptoms

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk Group</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Not reached</td>
</tr>
<tr>
<td>1-2</td>
<td>Intermediate-1</td>
<td>9.8</td>
</tr>
<tr>
<td>3-4</td>
<td>Intermediate-2</td>
<td>4.8</td>
</tr>
<tr>
<td>&gt;4</td>
<td>High</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Fig 1. Survival data on patients with primary myelofibrosis stratified by the revised MIPSS70+ version 2.0 (mutation- and karyotype-enhanced international prognostic scoring system for transplant-age patients). (A) Included 311 patients ≤ 70 years of age and (B) patients of all age groups. (C) Provides a graph for visual comparison of stratification by MIPSS70+. Risk point assignments were as follows: 4 points for very-high-risk karyotype; 3 points each for unfavorable karyotype and ≥ 2 high-molecular-risk mutations; 2 points each for only one high-molecular-risk mutation, absence of type 1-like CALR mutation, presence of constitutional symptoms, hemoglobin < 8 g/dL in women and < 9 g/dL in men; and one point each for hemoglobin level of 8 to 9.9 g/dL in women and 9 to 10.9 g/dL in men and ≥ 2% circulating blasts. Risk categories included very high risk, ≥ 9 points; high risk, 5 to 8 points; intermediate risk, 3 to 4 points: low risk, 1 to 2 points; and very low risk, no adverse points. Hazard ratios (95% CIs) in patients ≤ 70 years old were low versus very low risk, 7.2 (1.0 to 53.2); intermediate versus low risk, 2.1 (1.2 to 3.6); high versus intermediate risk, 2.2 (1.5 to 3.2); and very high versus high risk, 2.7 (1.8 to 4.0).

Published in: Ayalew Tefferi; Paola Guglielmelli; Terra L. Lasho; Naseema Gangat; Rhett P. Ketterling; Animesh Pardanani; Alessandro M. Vannucchi; Journal of Clinical Oncology 2018 361769-1770.
DOI: 10.1200/JCO.2018.78.9867
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Survival after Unrelated Donor HCT for MPNs, 2006-2016

- Myelofibrosis (n=969)
- Other MPN (n=1,300)

p=0.02
Survival after HLA-Matched Sibling Donor HCT for MPNs, 2006-2016

- Myelofibrosis (n=701)
- Other MPN (n=995)

p<0.001
## Myelofibrosis Transplant Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>N</th>
<th>Conditioning Regimen</th>
<th>Median Age</th>
<th>Median Follow-up</th>
<th>OS% (years)</th>
<th>NRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patriarca et al.</td>
<td>1986-2006</td>
<td>100</td>
<td>RIC and MAC</td>
<td>49</td>
<td>34 mon</td>
<td>42 (3)</td>
<td>43%</td>
</tr>
<tr>
<td>Balen et al.</td>
<td>1989-2002</td>
<td>289</td>
<td>RIC and MAC</td>
<td>47</td>
<td>41/46 mon</td>
<td>37/30 (5)</td>
<td>35/50%</td>
</tr>
<tr>
<td>Scott et al.</td>
<td>1990-2009</td>
<td>170</td>
<td>RIC and MAC</td>
<td>51</td>
<td>5.9 years</td>
<td>57 (5)</td>
<td>34%</td>
</tr>
<tr>
<td>Lussana et al.</td>
<td>1994-2010</td>
<td>250</td>
<td>RIC and MAC</td>
<td>56</td>
<td>13 mon</td>
<td>55 (3)</td>
<td>28%</td>
</tr>
<tr>
<td>Robin et al.</td>
<td>1997-2008</td>
<td>147</td>
<td>RIC and MAC</td>
<td>53</td>
<td>35 mon</td>
<td>39 (4)</td>
<td>39%</td>
</tr>
<tr>
<td>Gupta et al.</td>
<td>1997-2010</td>
<td>233</td>
<td>RIC</td>
<td>55</td>
<td>50 mon</td>
<td>47 (5)</td>
<td>24%</td>
</tr>
<tr>
<td>Kroger et al.</td>
<td>2002-2007</td>
<td>103</td>
<td>RIC Flu/Bu</td>
<td>55</td>
<td>33 mon</td>
<td>67 (5)</td>
<td>16%</td>
</tr>
</tbody>
</table>

At City of Hope an overwhelming majority of patients were treated with FluMel-based conditioning and tacrolimus/sirolimus-based GVHD prophylaxis.
Molecular profile of MF. (A) Mutations visualized as an oncoplot.


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Kaplan-Meier curves defining survival outcomes at 60 months after allo-HCT.

Kaplan-Meier curves demonstrating survival outcomes at 60 months after allo-HCT.

Kaplan-Meier survival analysis for (A) the entire patient cohort ($n = 75$, black line) and patients treated with curative ($n = 39$, gray line) and noncurative ($n = 36$, dashed line) intent.

Ruxolitinib reduces GVHD in patients with acute corticosteroid-refractory GVHD. All patients were refractory to steroids and at least 2 other lines of treatment of GVHD.

Spoerl S et al. Blood 2014;123:3832-3842
Aids to decision making in selection of initial therapy (drug therapy vs HCT) in patients with MF.

Figure 1

Total number of MF patients
n=129

Missing
n=9, (7%)

Those referred for transplant and went to appointment
n=41 (32%)

Those referred who did not go to appointment
n=8 (6%)

Those not referred for transplant
n=71 (59%)

Those who will proceed with transplant
n=16 (39%)

Those who won't proceed with transplant
n=24 (60%)
Optimization of allogeneic stem-cell transplantation in patients with myelofibrosis.

- Pretransplantation
  - Improve constitutional symptoms: *JAK inhibitor*
  - Reduce spleen size: *JAK inhibitor*
  - Reduce iron overload: *Chelation*

- Transplantation
  - Select intensity of conditioning regimen after balancing the risk of relapse and of NRM

- Post-transplantation
  - Monitor residual disease: *Molecular marker Chimerism*
  - Treat residual disease: *Reduce immunosuppression Donor lymphocyte infusion*

Nicolaus Kröger JOP 2016;12:629-631
Allogeneic Hematopoietic Stem Cell Transplantation for MF

HSCT is a reasonable option for otherwise healthy patients with intermediate-2 or high-risk PMF
• HSCT is the only potentially curative treatment approach
• Young, otherwise fit patients may be candidates

• Therapeutic efficacy is mediated via:
  – Antineoplastic effect of pre-transplant conditioning regimen
  – Alloimmune graft versus leukemia effect

• Reduced intensity conditioning may be considered for:
  – Older patients
  – Patients with comorbidities that preclude them from myeloablative conditioning regimens

Allogeneic Hematopoietic Stem Cell Transplantation for MF

- **Challenges**
  - Significant risk of treatment-related morbidity and mortality
  - Optimal timing of transplant
  - Patient selection (DIPSS Int-2 and High-risk)
  - Choice of conditioning regimen

- **Barriers to HCT success**
  - Regimen related-toxicities (hepatotoxicity)
  - Graft failure (poorly understood)
  - Acute and chronic graft versus host disease (GVHD)
  - Poor performance status (symptomatic splenomegaly, debilitating constitutional symptoms, anemia)

Unanswered Questions

1. Optimal Conditioning regimen
   Myeloablative; RIC- Flu/Mel; Flu/Bu; other

2. Source of stem cells- BM vs. PB; Donor- MUD/cord/Haplo

3. Optimal GVHD prophylaxis- Tacrolimus/MTX;
   Tacrolimus/sirolimus; +/- ATG; Post HCT Cy; T cell depletion

4. Prevention of SOS - Ursodiol; low dose heparin

5. Impact of Pulmonary fibrosis/hypertension on post HCT complications

6. Optimal timing of HCT- not too soon, not too late

7. Predictors of outcomes-DIPSS Plus? MIPSS?
   Splenectomy? Age? Donor?

8. Role of JAK2 Inhibitors pre- and post-HCT

9. Monitoring of MRD and early intervention with DLI