Advances in Autologous and Allogeneic HSCT: Key Contributions from 2018 ASBMT/CIBMTR Tandem Meeting

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Medical Director, Blood and Marrow Transplant
Department of Internal Medicine
The University of Kansas Medical Center
Conflicts of Interest

- KITE
- Novartis
Annual Number of HCT Recipients in the US by Transplant Type

- Autologous
- Allogeneic

Number of Transplants

Year:
- 1980
- 1984
- 1988
- 1992
- 1996
- 2000
- 2004
- 2008
- 2012
- 2016

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
Blood & Marrow Transplant – Annual Volume (CY)

Year

# of Transplants

Total
Auto
Allo


50 47 33 14 34 6 138 90 101 105 117 129 215 175 230 303 298 323 221 272 168 327

5 6 18 8 63 104 117 4 66 8 125 125 132 132 166 152 178 102 132 104 132

2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2
BMT Disease Indications (CY17)

Autologous
*(n=195)*

- MM: 64%
- NHL: 26%
- Other: 5%
- AML/ALL: <1%
- HD: 5%

Allogeneic
*(n=132)*

- AML: 36%
- MDS: 21%
- NHL: 12%
- ALL: 14%
- CLL/CML: 6%
- Other: 6%
- HD: 5%
Challenges to Improving Outcomes of Stem Cell Transplantations

1. Access
   a. Macroeconomics
   b. U.S. Socioeconomics
   c. Lack of Donors
   d. Advanced Age/Co-morbidities

2. Knowledge regarding indications and timely referral

3. Relapse

4. Graft-vs-Host Disease

5. Infection

6. Long-term survival and late effects
Global Development of HSCT, 2010

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Stem Cell Transplantation in AML and Socioeconomic Factors: National Cancer Data base (NCBD) Analysis

- N= 37,820
- 1998-2012
- 18-64 years of age (mean=47.3)
- Age 50-64 31% less likely to have SCT compared to 18-49
- Whites 50.2% more likely than Blacks
- Medicaid, Medicare are 29.5%, and 37.2% less likely
- Annual income >46K 53.9% more likely than <46k
- AML induction at academic facility 3x more likely to get SCT compared to those in community setting.
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The only option is an HSCT from a

1. Matched Unrelated Donor
2. Unrelated Cord Blood Unit
3. Mismatched family donor
Allogeneic HCT Recipients in the US, by Donor Type
Adjusted Probability of OS in Adult AML, by Donor Type

(n=2,223)

HLA-id Sib (n=624)

8/8 MUD (n=1,193)

7/8 MUD (n=406)

Comparing outcomes of matched related donor and matched unrelated donor hematopoietic cell transplants in adults with B-Cell acute lymphoblastic leukemia.

~1500 patients with ALL

Racial / Ethnic Distribution of Potential Donors in the NMDP Donor Registry

- White: 71%
- Hispanic: 10%
- African American/Black: 7%
- Asian: 7%
- Multiple race: 4%
- Native Hawaiian/Other Pacific Islander: <1%
- American Indian/Alaska Native: 1%
Umbilical Cord Blood Hypothesis

- Superior proliferative capacity will compensate for low cell dose
- Naïve immune system reduced GVHD ⇒ extension of donor pool
- Unlimited supply, rapid availability
Survival Based on Donor Source

Comparison of transplant outcomes from matched sibling bone marrow or peripheral blood stem cell and unrelated cord blood in patients 50 years or older

Japanese Registry Data (AML, ALL, MDS)
- > 50 years old
- 2000 patients
- OS @ 2 years
  - BMT- 53.5%
  - PBSCT- 47%
  - CBT- 36.1%
  - P<0.001

Alternative Donor Availability

Genetic Haploidentity

- **All Patients Donor Found**
- **Caucasian Transplant Available**
- **Non-Caucasian Transplant Available**

Range

- **5-6/6**
- **4/6**
- **3/6**
Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts

Figure 4. Actuarial survival of patients stratified for donor type. Overall there is no statistically significant difference in survival.

Transplants by Ethnic Background

Source: National Marrow Donor Program/Be The Match FY 2016
## Alternative Donor Transplantation Pros & Cons

<table>
<thead>
<tr>
<th></th>
<th>Availability to patient</th>
<th>Timing</th>
<th>Acquisition cost</th>
<th>Comments</th>
<th>Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUD</td>
<td>60%</td>
<td>3-4 mos</td>
<td>$35K</td>
<td>Long track record</td>
<td>1. Relapse during search</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Availability to some ethnic groups (eg. AAs)</td>
</tr>
<tr>
<td>Cord</td>
<td>&gt;90%</td>
<td>6 wks</td>
<td>$29-50K/ per unit</td>
<td>1. No donor concerns</td>
<td>1. Low stem cell #s</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Young HSCs</td>
<td>2. Low memory T cell #s &amp; immune reconstitution</td>
</tr>
<tr>
<td>Haplo</td>
<td>&gt;95%</td>
<td>4 wks</td>
<td>$10K</td>
<td>1. Low TRM</td>
<td>1. Historical GVHD/ mortality rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Excellent immune reconstitution</td>
<td>2. Relapse rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. DLI possibility</td>
<td></td>
</tr>
</tbody>
</table>

Personal Communications: R. Jones (Johns Hopkins)

CTN 1101
Challenges to Improving Outcomes of Stem Cell Transplantations

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Incidence of Blood Cancers

![Graph showing the incidence of blood cancers by age group and type. The graph includes data for AML, ALL, CML, CLL, and MDS.]
Acute Myeloid Leukemia

- >50% of patients achieve remission but chemotherapy is not curative for most patients
- Outcomes are poor for patients over age 60

Overall Survival Patients Older Than 55 years

Forman, S. J. Hematology 2009:406-413

Increasing Use of Allogeneic HCT in Patients Age 70 Years and Older: A CIBMTR Study of Trends and Outcomes (Abstract # 67)

**Figure 1:** Absolute number of allogeneic transplants in recipients 70 years and older from 2000 to 2013 reported to the CIBMTR by disease category.

**Figure 2:** OS for allogeneic HCT recipients 70 years and older transplanted between 2000-2007 and 2008-2013.

BMT Tandem 2017# 87 - Allogeneic Hematopoietic Cell Transplantation (HCT) in the Eighth Decade of Life: How Much Does Age Matter?

- 1637 consecutive patients
- non-myeloablative HCT 1997 - 2015
- 2 year OS, PFS, Rel., NRM

<table>
<thead>
<tr>
<th>Age - Years</th>
<th>OS</th>
<th>PFS</th>
<th>Relapse</th>
<th>NRM</th>
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</thead>
<tbody>
<tr>
<td>20-39</td>
<td>66</td>
<td>46</td>
<td>34</td>
<td>18</td>
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<tr>
<td>40-49</td>
<td>62</td>
<td>52</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>50-59</td>
<td>53</td>
<td>42</td>
<td>35</td>
<td>23</td>
</tr>
<tr>
<td>60-69</td>
<td>56</td>
<td>45</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>70-79</td>
<td>55</td>
<td>46</td>
<td>35</td>
<td>19</td>
</tr>
</tbody>
</table>
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Causes of Death after Transplants 2014-2015

**Autologous**

- Primary Disease: 69%
- Infection: 15%
- Organ Failure: 7%
- Second Malignancy: 7%
- Hemorrhage: 6%
- Other: 2%

**HLA-identical Sibling**

- Primary Disease: 58%
- Infection: 17%
- Organ Failure: 9%
- Graft Rejection: 7%
- Second Malignancy: 7%
- Hemorrhage: 6%
- Other: 1%

**Unrelated Donor**

- Primary Disease: 47%
- Infection: 20%
- GVHD: 13%
- Organ Failure: 10%
- Second Malignancy: 8%
- Hemorrhage: 7%
- Other: 1%

*Data reflects 3-year mortality*
Trends in survival after Autologous HCT for Multiple Myeloma, 2001-2014

- 2001-2004 (n=9,287)
- 2005-2008 (n=11,092)
- 2009-2012 (n=18,066)
- 2013-2014 (n=10,553)

p<0.001
Strategies to improve outcomes in Multiple Myeloma

• Post SCT Maintenance
• Post SCT consolidation → maintenance
  – CTN 0702

Immunotherapeutic strategies for MRD

Source: David Avigan, MD; Beth Israel Deaconess Medical Center
DC/MM Fusion Vaccination in Conjunction with Autologous Transplantation

• Number Enrolled: 45
  – 80% Male, 20% Female
• Number Received Vaccine: 35
• Median Age at Enrollment: 58
• Median Bone Marrow Involvement at Enrollment: 55% plasma cells
• Median Time from Transplant to Post-Transplant Vaccine: 48 days

Rosenblatt, et al. CCR 2013
Vaccination Induced Expansion of MM reactive T cells and Targeting of MRD

Rosenblatt et al. CCR 2013
BMT CTN Protocol 1401

Phase II Multicenter Trial of Single Autologous Hematopoietic Cell Transplant Followed by Lenalidomide Maintenance for Multiple Myeloma with or without Vaccination with Dendritic Cell (DC)/Myeloma Fusions (MY T VAX)

David Avigan, Nina Shah, David Chung, Marcelo Pasquini
Survival after HLA-Matched Sibling Donor HCT for AML, 2005-2015

- Early (n=8,254)
- Intermediate (n=2,089)
- Advanced (n=2,766)

p < .0001
Timing Matters

“Early referral is perhaps the single most important step that can affect survival.”

Patients transplanted earlier in their disease have better outcomes than patients with advanced disease, regardless of the degree of match.

Acute Leukemia Hotline

888-588-1167

• Streamlined access to the on-call leukemia physician
• Facilitate patient transfers
• Updated information on clinical trials
Dendritic Cell/AML Fusions: A Personalized Vaccine

- CD117
- MUC-1
- WT1
- PR1
- CD54
- CD80
- CD83
- CD40L
- CD86
- HLA Class II
- HLA Class I
- Tumor Activated Peptide
- CD4+ T Cell
- CD80, 86, 40L, 54
- CD83
- CD80, 86, 40L, 54
- Activation Helper Cytokines
- DC/AML Fusion Cell
- CD8+ T Cell
- Activation CTL
Acute Myeloid Leukemia

• >50% of patients achieve remission but chemotherapy is not curative for most patients
• Outcomes are poor for patients over age 60

Overall Survival Patients Older Than 55 years

Forman, S. J. Hematology 2009:406-413

Clinical Outcomes

• 12 of 17 patients who received at least one dose of vaccine remain alive and in remission (71%; 90% CI, 52 to 89%) at 16.7 to 66.5 months from initiating vaccination
• Median follow-up: 57 months
FLT3/ITD AML Through the Years

2005

Percent survival

Months

2012-2020

BMT- CTN 1506
Phase 3 randomized study of FLT3 inhibition post-allogeneic transplant

2011

Benefit of allogeneic transplant

Overall Survival of FLT3 ITD AML

2016

Benefit of post BMT FLT3 TKI maintenance

BMT not on J11116
J11116 (BMT+ Sorafenib)

NCI
Designeated Cancer Center

THE UNIVERSITY OF KANSAS CANCER CENTER

44
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Causes of Mortality related to Allogeneic BMT

**HLA-identical Sibling 2014-2015**

- Died at or beyond 100 days post-transplant*
  - Primary Disease: 58%
  - Infection: 17%
  - Organ Failure: 9%
  - GVHD: 7%
  - Graft Rejection: 7%
  - Second Malignancy: 1%
  - Hemorrhage: 1%
  - Other: 1%

*Data reflects 3-year mortality

**Unrelated Donor 2014-2015**

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  - Primary Disease: 47%
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* Data reflects 3-year mortality
Prevention Strategies

1. Drugs: CNI, anti-metabolites, steroids, M-TOR
2. T Cell depletion in vivo / ex vivo
3. Stem Cell source: BM vs P.B.
4. T Cell homing-Interference
5. Post-Transplant Cytoxan

BMT- CTN 1301
Dynamic Graft-Versus-Host Disease-Free, Relapse-Free Survival (dGRFS): Multistate Modeling of the Morbidity and Mortality of Allotransplantation

- 949 patients
- 1st allogeneic HCT for hematologic malignancies at the University of Minnesota between 2000-2013
- Median age = 43
- Best dGRFS at 1 year
  - Matched sibling donor BM (64.9%)
  - followed by UCB (41.7%)
  - URD BM (35.8%)
  - matched sibling PBSC (23.4%)
  - URD PBSC (12.5%)
# Acute GVHD - Treatment

- Steroids
- Infliximab
- Photopheresis
- Sirolimus
- Azathioprine
- Thalidomide
- PUVA
- Campath-1H
- ATG
- Tacrolimus / CSA
- Mycophenolate
- Etanercept
- Plaquenil
- Pentostatin
- Clofazimine
- MSC

## Problems:
- Steroid refractory aGvHD very high mortality
- High dose steroids numerous side effects especially in the elderly
Overall Survival in Steroid-Responsive and Refractory aGVHD

Steroids Versus Steroids Plus Additional Agent in Frontline Treatment of Acute Graft-versus-Host Disease: A Systematic Review and Meta-Analysis of Randomized Trials of Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>aGVHD Requirement</th>
<th>Experimental Agent</th>
<th>Severe aGVHD at Enrollment</th>
<th>Prior GVHD Prophylaxis</th>
<th>Prior Steroid Exclusion Criteria</th>
<th>Completed</th>
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</thead>
<tbody>
<tr>
<td>Cahn, 1995</td>
<td>69</td>
<td>Grade III-IV</td>
<td>BT563</td>
<td>No grade IV</td>
<td>CsA or CsA/MTX</td>
<td>None allowed</td>
<td>Yes</td>
</tr>
<tr>
<td>Martin, 1996</td>
<td>243</td>
<td>Grade II-IV</td>
<td>CD5 immunotoxin</td>
<td>NA</td>
<td>CsA/MTX: 84% Cont. through Rx</td>
<td>None allowed</td>
<td>Yes</td>
</tr>
<tr>
<td>Van Lint, 1998</td>
<td>93</td>
<td>Grade II-IV</td>
<td>MP 10 mg/kg/day</td>
<td>NA</td>
<td>CsA: 53%</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Cragg, 2000</td>
<td>96</td>
<td>Grade II-IV</td>
<td>ATG</td>
<td>5% (no grade IV)</td>
<td>CsA/MTX: 47%</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Lee, 2004</td>
<td>102</td>
<td>Grade II-IV</td>
<td>Daclizumab</td>
<td>20%</td>
<td>Na</td>
<td>&gt;1 mg/kg/d within 7 d</td>
<td>No</td>
</tr>
<tr>
<td>Couriel, 2009</td>
<td>57</td>
<td>Grade II-IV</td>
<td>Infliximab</td>
<td>33%</td>
<td>Tac/MTX: 88%</td>
<td>&gt;2 d and &gt;2 mg/kg/d</td>
<td>No</td>
</tr>
<tr>
<td>Bolanos-Meade, 2014</td>
<td>235</td>
<td>Requiring systemic Rx</td>
<td>MMF</td>
<td>33%</td>
<td>No prior MMF allowed within 7 d</td>
<td>&gt;3 d and &gt;.5 mg/kg/d</td>
<td>No</td>
</tr>
</tbody>
</table>
Mechanisms of MSC Suppression

**Inhibition:**

Direct contact dependent
- B7-H1

Indirect Cytokine-mediated
- PGE2
- Cox 1 & 2
- HGF
- TGF-B
- IL-10
- HLA G & E
- LIF
- IDO

Exosome- mediated

---

Fig. 1 – Schematic illustration of the effects of MSCs on the immune system. NK, B, and T refer to NK, B, and T cells, respectively. DC1: mature monocyctic dendritic cells; DC2: mature plasmacytic dendritic cells.

Wharton’s Jelly Cells – the MSCs of the Umbilical Cord

Umbilical cord is not biohazardous waste.
It is a gold mine!

Source: Mark Weiss
Isolation, Culture and Expansion of WJ-MSCs

- **Harvest WJ-MSCs with enzymes, dilute and continue expansion**

- **Umbilical cord is washed to remove all traces of blood, & the blood vessels removed**

- **WJ-MSCs growing in a sterile, closed growth chamber (4-5B WJ-MSCs)**

- **WJ-MSCs growing in a sterile, plastic flask (50-70M WJ-MSCs)**

- **WJ-MSCs migrating out of Wharton’s Jelly (≈ 30M WJ-MSCs/cord)**

Source: Jim Mitchell, PhD
Xenograft GvHD Model

PBMCs from healthy donor

MSCs from Wharton's Jelly

NSG mice
GvHD Scoring System

- Weight loss
- Posture
- Activity
- Ruffling
- Skin integrity

Based on Cooke, et. al. Blood 88: 3230
Slides provided by Tom Yankee, Pharm.D, PhD
Investigator Initiated Trial
IIT-2016-aGvHD-MSCTC-0010

A Phase I Study To Evaluate the Safety of Umbilical Cord – Derived, Ex-Vivo Cultured and Expanded Wharton’s Jelly Mesenchymal Stem Cells for the Treatment of De Novo High Risk Acute or Steroid Refractory Acute Graft Versus Host Disease
Midwest Stem Cell Therapy Center
Jim Mitchell, Ph.D.
Rupal Soder, Ph.D.
Zhuo Tang, M.D.
Robert Vincent

Department of Microbiology, Molecular Genetics, and Immunology
Thomas Yankee, Pharm.D., Ph.D.
Amara Seng
John Szarejko

HMCT and KUCC
Joseph McGuirk, D.O.
Sunil Abhyankar, M.D.
Neil Dunavin, M.D.
Scott Weir, Pharm.D., Ph.D.
Kevin Schorno, M.B.A.
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Neutropenia, mucositis and aGvHD and cGvHD

**Host immune system defect**
- Phase I, Pre-engraftment, < 30 days: Neutropenia, mucositis and aGvHD
- Phase II, Post-engraftment, 30 - 100 days: Neutropenia, mucositis and aGvHD and cGvHD
- Phase III, Late phase, > 100 days: Impaired cellular and humoral immunity and cGvHD

**Device risk**
- Central line (continuous risk)

**Allogeneic patients**
- Respiratory and enteric viruses: Herpes simplex virus, Epstein-Barr virus lymphoproliferative ds, Cytomegalovirus, Varicella-zoster virus, Epstein-Barr virus lymphoproliferative ds
- GI tract: Staphlococcus epidermidis, Streptococci species, All Candida species
- Encapsulated bacteria (eg., pneumococcus)
- Aspergillus species
- Pneumocystis carinii
- Toxoplasma gondii
- Strongyloides stercoralis

**KEY:**
- High incidence
- Low incidence
- Episodic
CAR T – other CD19+ targets

CAR T Multivalent CTL

CAR T- Multivalent

CAR T- Solid Tumors

- DLBCL
- MCL
- Follicular
- Multiple Myeloma
- *other Hem Targets (e.g. CD\textsubscript{33})

- EBV
- Adenovirous
- BK
- RSV
- CMV

- Virus
- Tumor
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Long Term Survival after HCT

**Overall Survival**

Probability of OS (%)

Time Since Transplant (years)

**Non-relapse mortality**

Cumulative Incidence of NRM (%)

Time Since Transplant (years)

Thank You!