Advances in Stem Cell Transplantation and Advancements in Cellular Therapeutics

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Conflict of Interest

• No conflicts to declare
Annual Number of HCT Recipients in the US by Transplant Type

- Autologous
- Allogeneic

Number of Transplants

- 0
- 2000
- 4000
- 6000
- 8000
- 10000
- 12000
- 14000
- 16000

Years


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

Total Transplants

- 2006: 47
- 2007: 90
- 2008: 138
- 2009: 164
- 2010: 179
- 2011: 215
- 2012: 230
- 2013: 303
- 2014: 298
- 2015: 323
- 2016: 272
Indications for Hematopoietic Cell Transplant in the US, 2014

- Allogeneic (Total N=8,211)
- Autologous (Total N=12,831)

Number of Transplants

- Myeloma / PCD
- NHL
- AML
- HD
- ALL
- MDS / MPN
- CLL
- Other Cancer
- CML
- Aplastic Anemia
- Other Non-Malignant Disease
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
“One million haemopoietic stem-cell transplants: a retrospective observational study”

Volume 2, No. 3, e91-e100, March 2015

Prof Alois Gratwohl, MD, Marcelo C Pasquini, MD, Prof Mahmoud Aljurf, MD, Yoshiko Atsuta, MD, Helen Baldomero, BMS, Lydia Foeken, MD, Michael Gratwohl, PhD, Prof Luis Fernando Bouzas, MD, Dennis Confer, MD, Karl Frauendorfer, PhD, Prof Eliane Gluckman, MD, Prof Hildegard Greinix, MD, Prof Mary Horowitz, MD, Minako Iida, MD, Prof Jeff Lipton, MD, Alejandro Madrigal, MD, Prof Mohamad Mohty, MD, Luc Noel, MD, Prof Nicolas Novitzky, MD, José Nunez, MD, Machteld Oudshoorn, PhD, Prof Jakob Passweg, MD, Prof Jon van Rood, MD, Prof Jeff Szer, MD, Prof Karl Blume, MD, Prof Frederic R Appelbaum, MD, Prof Yoshihisa Kodera, MD, Prof Dietger Niederwieser, MD, for the Worldwide Network for Blood and Marrow Transplantation (WBMT)
Global Development of HSCT, 2010

Challenges to Improving Outcomes of Stem Cell Transplantations

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

ASBMT 2016 Abstract # 17
Samip Master, Srinivas Devarakonda, Glenn Mills, and Runhua Shi

- 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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Probability of Having a Donor Match

The only option is an HSCT from a

- Matched Unrelated Donor
- Unrelated Cord Blood Unit
- Mismatched family donor
Allogeneic HCT Recipients in the US, by Donor Type

- HLA-identical sibling
- Other relative, ≥2 HLA antigen mismatch
- URD-BM/PB
- Other relative, 1 HLA antigen mismatch
- Other relative, HLA-match unknown
- URD-CB

Number of Transplants


CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
Adjusted Probability of OS in Adult AML, by Donor Type

©2012 by American Society of Hematology
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

1. Superior proliferative capacity will compensate for low cell dose

2. Naïve immune system reduced GVHD → extension of donor pool

3. Unlimited supply, rapid availability
Survival Based on Donor Source

Alternative Donor Availability

- Genetic Haploidentity
  - 5-6/6
  - 4/6
  - 3/6

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

Range
# Alternative Donor Transplantation Pros and Cons

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

**Think: CTN 1101**

Personal Communications: R. Jones (Johns Hopkins)
Challenges to Improving Outcomes of Stem Cell Transplantations

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6. Long-term survival and late effects
Incidence of Blood Cancers

Rate per 100,000 Population

Ages
AML in Older Patients

Rowe et al. Blood 103:479-485, 2004
Increasing Use of Allogeneic HCT in Patients Age 70 Years and Older: A CIBMTR Study of Trends and Outcomes (Abstract # 67)

Lori Muffly, Marcelo Pasquini, Michael Martens, Ruta Brazauskas, Xiaochun Zhu, Kehinde Adekola, Mahmoud D. Aljurf, Andrew S. Artz, et al

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.
Challenges to Improving Outcomes of Stem Cell Transplantations

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Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation

INITIAL PUBLICATION AUGUST 6, 2015 - LAST UPDATED AUGUST 6, 2015

DEFINITIONS

Definitions for Classifying Indications

INDICATIONS FOR HCT IN PEDIATRIC PATIENTS...

- Leukemia / MDS
- Lymphoma
- Solid Tumors
- Nonmalignant Diseases
Challenges to Improving Outcomes of Stem Cell Transplantations

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Causes of Death after Transplants 2012-2013

**HLA-identical Sibling**
- Primary Disease: 48%
- GVHD: 16%
- Infection: 14%
- Organ Failure: 17%
- Second Malignancy: 1%
- Other: 1%

**Unrelated Donor**
- Primary Disease: 37%
- GVHD: 20%
- Infection: 17%
- Organ Failure: 6%
- Second Malignancy: 1%
- Other: 20%

**Autologous**
- Primary Disease: 70%
- Infection: 20%
- Organ Failure: 7%
- Second Malignancy: 1%
- Other: 1%
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
Survival after HLA-Matched Sibling Donor HCT for AML, 2004-2014

- Early (n=8,154)
- Intermediate (n=2,131)
- Advanced (n=2,833)

p<0.001
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.

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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

[Diagram showing interactions between DC, AML, and T cells]

- DC express HLA Class II, CD80, 86, 40L, 54.
- AML express HLA Class II, MUC-1, PR1, CD117.
- Tumor Activated Peptide binds to HLA Class I.
- CD4+ T Cell activated by helper cytokines.
- CD8+ T Cell activated by CTL.
Clinical Outcomes

- Median age was 63 years
- 12 of 17 patients who received at least one dose of vaccine remain alive and in remission
- Median follow-up: 57 months
Effect of T-Cell Depletion and GVHD on Probability of Relapse in Leukemia

DLI

- Marrow aplasia
- GVHD
- Poor efficacy

TIL + IL2– e.g. melanoma

- HLA-restricted
- Mis-pairing α and β chain
- Doesn’t recognize glycolipids or carbohydrates

TCR – modification

CAR T Cells (not HLA restricted)
Optimizing the CAR Signaling Domain to Treat Hematologic Malignancies

Recognition Domain

Signaling Domains

\( V_H \)

\( V_L \)

Hinge/spacer

CD28, 4-1BB, OX40

(Signal 2)

CD3\( _\zeta \) (Signal 1)


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Schematic of the Treatment of a Patient with Chimeric Antigen Receptor (CAR) T Cells

1) T Cell Collection

2) T Cell Transfection
   1. Binding
   2. Fusion

3) T Cell Adoptive Transfer
   3. Integration
   4. Transcription and protein expression
   5. CAR cell membrane insertion

4) Patient Monitoring
   a) Disease response
      - CT scans
      - Bone marrow biopsies
      - Peripheral blood flow cytometry
   b) CAR-T Cell persistence
      - Immunohistochemistry of bone marrow biopsy
      - RT-PCR and flow cytometry of blood and bone marrow aspirate

Jacobson C A and Ritz J Blood 2011;118:4761-4762
©2011 by American Society of Hematology
CD19: An Ideal Tumor Target in B-Cell Malignancies

- **CD19 expression is generally restricted to B cells and B cell precursors**\(^1\)
  - CD19 is not expressed on hematopoietic stem cells\(^1\)
- **CD19 is expressed by most B-cell malignancies**\(^1\)
  - CLL, B-ALL, DLBCL, FL, MCL\(^1\)
- **Antibodies against CD19 inhibit tumor cell growth**

Outcomes for Adults with 1st Relapse ALL

Outcomes for Adults with Relapsed ALL after Allogeneic SCT

Poon, et al. BBMT 2013;19, 1064
Original Article
Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

<table>
<thead>
<tr>
<th>Response</th>
<th>N=30</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>27/30</td>
<td>90%</td>
</tr>
<tr>
<td>No response</td>
<td>3/30</td>
<td>10%</td>
</tr>
<tr>
<td>Not evaluable extramedullary dz (1) and short f/u (2)</td>
<td>3/30</td>
<td>10%</td>
</tr>
</tbody>
</table>
Toxicity: CTL019

- No significant acute infusional toxicity
- Tumor lysis syndrome
  - Reversible and manageable
- B cell aplasia and hypogammaglobulinemia
  - Supported with intravenous immunoglobulin (IVIG)
  - No excessive or frequent infections
- Cytokine Release Syndrome (CRS)
- Neurotoxicity

Kite Announces Positive Topline Primary Results of Axicabtagene Ciloleucel from First Pivotal CAR-T Trial in Patients with Aggressive Non-Hodgkin Lymphoma

One hundred one patients were treated in ZUMA-1.

<table>
<thead>
<tr>
<th></th>
<th>DLBCL (n=77)</th>
<th>TFL/PMBCL (n=24)</th>
<th>Combined (n= 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (%)</strong></td>
<td><strong>CR (%)</strong></td>
<td><strong>ORR (%)</strong></td>
<td><strong>CR (%)</strong></td>
</tr>
<tr>
<td>ORR</td>
<td>82</td>
<td>49</td>
<td>83</td>
</tr>
<tr>
<td>Month 6</td>
<td>36</td>
<td>31</td>
<td>54</td>
</tr>
</tbody>
</table>

http://ir.kitepharma.com/releasedetail.cfm?ReleaseID=1014817
Targeting AML: CD33 and CD34 as differentiation antigens

- CD33 antigen expressed on ~88% of AML\(^1\)
- Not expressed by multipotent hematopoietic progenitor cells\(^2\)
- Minimal expression on non-hematopoietic normal cells

Generation of Transgene and Function of Activated iCasp9

## Characteristics of Patients & Clinical Outcomes

<table>
<thead>
<tr>
<th>Pt#</th>
<th>Gender (age in yrs)</th>
<th>Diagnosis</th>
<th>Disease status at SCT</th>
<th>Conditioning/Intensity*</th>
<th>Infused CD34/kg</th>
<th>Infused CD3/kg</th>
<th>Days from SCT to T-cell infusion</th>
<th>Infused T cells/kg</th>
<th>aGVHD</th>
<th>cGVHD</th>
<th>Administration of AP1903</th>
<th>Current status (day after SCT†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M (3)</td>
<td>Secondary AML</td>
<td>CR2</td>
<td>Bu-Flu-Campath/MAC</td>
<td>$1.2 \times 10^7$</td>
<td>$8.2 \times 10^4$</td>
<td>66</td>
<td>$1 \times 10^6$</td>
<td>Grade I/II</td>
<td>None</td>
<td>Yes</td>
<td>Alive, CR (D+ 1440)</td>
</tr>
<tr>
<td>2</td>
<td>F (17)</td>
<td>B-ALL</td>
<td>CR2</td>
<td>Bu-Cy-Campath/MAC</td>
<td>$1.0 \times 10^7$</td>
<td>$3.8 \times 10^4$</td>
<td>80 and 111</td>
<td>$1 \times 10^6$</td>
<td>Grade I</td>
<td>None</td>
<td>Yes</td>
<td>Relapse of ALL (D+ 552), death D+ 591</td>
</tr>
<tr>
<td>3</td>
<td>M (8)</td>
<td>T-ALL</td>
<td>PIF-CR1</td>
<td>AraC-Cy-Campath-TBI/MAC</td>
<td>$1.3 \times 10^7$</td>
<td>$1.7 \times 10^5$</td>
<td>93</td>
<td>$3 \times 10^6$</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Alive, CR (D+ 1388)</td>
</tr>
<tr>
<td>4</td>
<td>F (4)</td>
<td>T-ALL</td>
<td>Active disease</td>
<td>Bu-Cy-Campath/MAC</td>
<td>$1.6 \times 10^7$</td>
<td>$5.5 \times 10^4$</td>
<td>30</td>
<td>$3 \times 10^6$</td>
<td>Grade I</td>
<td>None</td>
<td>Yes</td>
<td>Relapse of ALL (D+ 57), death D+ 158</td>
</tr>
<tr>
<td>5</td>
<td>M (6)</td>
<td>B-ALL</td>
<td>CR2 (7q31 del)</td>
<td>AraC-Cy-Campath-TBI/MAC</td>
<td>$1.5 \times 10^7$</td>
<td>$0.4 \times 10^4$</td>
<td>42</td>
<td>$1 \times 10^7$</td>
<td>Grade I</td>
<td>None</td>
<td>Yes</td>
<td>Relapse of ALL (D+ 158), death D+ 164</td>
</tr>
<tr>
<td>6</td>
<td>F (17)</td>
<td>Biphenotypic leukemia</td>
<td>CR2</td>
<td>Flu-Mel-Campath/RIC</td>
<td>$0.8 \times 10^7$</td>
<td>$0.3 \times 10^4$</td>
<td>87</td>
<td>$1 \times 10^6$</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Alive, CR (D+ 1016)</td>
</tr>
<tr>
<td>7</td>
<td>F (7)</td>
<td>T-cell lymphoblastic lymphoma</td>
<td>CR2</td>
<td>HDAC-Cy-Campath-TBI/cranial XRT/MAC</td>
<td>$1.3 \times 10^7$</td>
<td>$0.9 \times 10^4$</td>
<td>75 and 368</td>
<td>$1 \times 10^7$</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Alive, CR (D+ 954)</td>
</tr>
<tr>
<td>8</td>
<td>M (14)</td>
<td>T-ALCL</td>
<td>CR1</td>
<td>AraC-Cy-Campath/MAC</td>
<td>$1.2 \times 10^7$</td>
<td>$0.3 \times 10^4$</td>
<td>40</td>
<td>$1 \times 10^7$</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Alive, CR (D+ 835)</td>
</tr>
<tr>
<td>9</td>
<td>F (9)</td>
<td>MDS monosomy 7</td>
<td>No excess blasts</td>
<td>Flu-Campath-TBI/RIC</td>
<td>$2.2 \times 10^7$</td>
<td>$0.5 \times 10^4$</td>
<td>90 and 271</td>
<td>$1 \times 10^6$</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Relapse (D+ 312) alive, CR (D+ 475) (second allo-HSCT)</td>
</tr>
<tr>
<td>10</td>
<td>F (8)</td>
<td>Biphenotypic leukemia</td>
<td>CR1</td>
<td>AraC-Cy-TBI/MAC</td>
<td>$1.5 \times 10^7$</td>
<td>$0.6 \times 10^4$</td>
<td>124 and 248</td>
<td>$1 \times 10^7 5 \times 10^6$</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Death from respiratory failure secondary to refractory AIHA (D+ 615)</td>
</tr>
</tbody>
</table>
Rapid Reversal of GVHD after Treatment with AP1903

A  Bilirubin Levels in Patient 1

B  Rash in Patient 2

FLT3/ITD AML Through the Years

Beat this, shiny new CARs

2005

Percent survival

Months

Hopkins

AMLSG

2011

Benefit of allogeneic transplant

Overall Survival of FLT3 ITD AML

Years

BMT- CTN 1506

Phase 3 randomized study of FLT3 inhibition post-allogeneic transplant

2012-2020

Benefit of post BMT FLT3 TKI maintenance

2016

J11116 (BMT+Sorafenib)

BMT not on J11116
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Causes of Mortality related to Allogeneic BMT

**HLA-identical Sibling 2012-2013**

- Primary Disease: 48%
- GVHD: 14%
- Infection: 17%
- Organ Failure: 16%
- Second Malignancy: 1%
- Other: 1%

**Unrelated Donor 2012-2013**

- Primary Disease: 37%
- GVHD: 20%
- Infection: 6%
- Organ Failure: 17%
- Second Malignancy: 1%
- Other: 1%
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 monocytic dendritic cells; DC2: mature plasmacytoid dendritic cells.
Isolation, Culture and Expansion of WJ-MSCs

- WJ-MSCs migrating out of Wharton's Jelly (≈ 30M WJ-MSCs/cord)
- Umbilical cord is washed to remove all traces of blood, & the blood vessels removed
- Harvest WJ-MSCs with enzymes, dilute and continue expansion
- 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
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
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Neutropenia, mucositis and aGvHD

**Impaired cellular and humoral immunity and cGvHD**

**Host immune system defect**

**Device risk**

**Allogeneic patients**

**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

- Central line
- (continuous risk)

**Respiratory and enteric viruses**
- Herpes simplex virus
- Cytomegalovirus
- Varicella-zoster virus
- Epstein-Barr virus lymphoproliferative ds

**Facultative Gram-neg. bacilli**
- Staphlococcus epidermidis

**GI tract Streptococci species**
- All Candida species
- Aspergillus species

**Aspergillus species**

**Pneumocystis carinii**

**Encapsulated bacteria** (eg., pneumococcus)

**Strongyloides stercoralis**

**KEY:**
- High incidence
- Low incidence
- Episodic

Days after transplant: 0, 30, 100, 360
CAR T – other CD19+ targets

CAR T

CAR T-Multivalent

CAR T-Solid Tumors

• DLBCL
• MCL
• Follicular
• Multiple Myeloma
• *other Hem Targets (e.g. CD_{33})

• EBV
• Adenovirous
• BK
• RSV
• CMV

• Virus
• Tumor
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
Long Term Survival after HCT

Overall Survival

Non-relapse mortality

Thank You!