Allogeneic Hematopoietic Stem Cell Transplantation: State of the Art in 2017

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Allogeneic Transplants Can Cure Hematological Malignancies that are Incurable with Conventional Chemotherapy

Pre-transplant intensive therapy

1) Conditioning Regimen

2) Graft-vs-Tumor

Transplant Day 0

Allograft (PBSC + Lymphs)

Remission

T-Cells

GVL

Leukemia cells
Graft-vs-Tumor Effects After Reduced Intensity Allogeneic Hematopoietic Cell Transplantation Can Cure
T-cell Mediated Graft-Vs-Leukemia Effects After HCT Can Cure Chemotherapy Resistant Malignancies

May 2006
1 month post transplant
On CSA

NHLBI Hematology Branch Transplant Protocol 02-H-0250
Major Improvements in Transplant Outcomes Over the Past 2 Decades

**Historical Problem**
- Conditioning regimens too toxic
- Older patients ineligible due to prohibitive risk of mortality

- Development of safer conditioning regimens (IV busulfan)/use of lung shielding
- Development of reduced intensity conditioning regimens
- Advent of voriconazole, PCR to detect early CMV reactivation with use of empiric gancyclovir. Letermovir for Cytomegalovirus Prophylaxis
- Growth of unrelated registry, increasing use MUDS, cord transplants and haploidentical donors
Improving Transplant Outcome for Severe Aplastic Anemia (SAA)

Overall Survival

Years after transplant

2001-2009 (n=1951)
1990-2000 (n=1377)
1981-1989 (n=701)
1975-1980 (n=142)

79%  73%  60%  34%

SAA-Severe Aplastic Anemia  IST-Immunosuppressive Therapy

Passweg JR et al. ASH Educ book 2010 (p 36-42)
Improving transplant outcome

One-Year Survival, percent


HLA-matched sibling
URD-unrelated donor

Better supportive care
Gentler conditioning
Improved mgmt of GVHD

Pasquini MC, Wang Z. CIBMTR
Most Common Indications for an Hematopoietic Cell Transplant (HCT) in the U.S.

Auto:
1. Myeloma
2. NHL

Allogeneic:
1. AML
2. ALL
3. MDS/MPD
Availability of a Stem Cell Sources for Allogeneic Transplantation

Chances of Finding a Stem Cell Donor

<table>
<thead>
<tr>
<th>HLA Matched Sibling</th>
<th>HLA Matched Unrelated Donor</th>
<th>No HLA Matched Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>10%</td>
<td>20%</td>
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<tr>
<td>30%</td>
<td>40%</td>
<td>50%</td>
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<tr>
<td>60%</td>
<td>70%</td>
<td>80%</td>
</tr>
<tr>
<td>90%</td>
<td>100%</td>
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</tbody>
</table>

Potential Candidates
For a Cord Blood Transplant or
A Haploidentical Transplant
Likelihood of Finding an 8/8 HLA Matched Unrelated Donor

- Unrelated donors now more than 20 million volunteers worldwide registered
- Age cut-off 60 years

Based on Current Donor Availability and with Recruitment Trends Extended to 2017.

Unrelated Cord Blood Transplantation (UCBT)

Unrelated Cord Blood (UCB) transplants are a transplant option for patients lacking an HLA identical donor:
- Cord blood is a rich source of Hematopoietic progenitor cells - more than human BM

Advantages of Cord Blood

- Lower Graft vs. Host Disease (GVHD)
- HLA-mismatched Transplants Possible
- Off the shelf product quickly available
- Cord Grafts available to Patients with Rare HLA Types And Ethnic Minorities
80% of adult patients of any ethnicity will have a cord unit that is suitable for transplantation

HLA match at least a 4/6 and TNC cell dose at least 2.5 x 10^7/kg (data from the NMDP)
Survival Following Cord Blood Transplantation: Allele Level Match Impacts Risk of TRM


Eapen et al Blood 2014;123;1
Status of Cord Blood Banking and Transplantation

2015: Approximately 37,000 CB transplants performed to date
- 2,000 + UCB transplants performed annually
- Almost 600,000 cord units in the world-wide public registry

Cord-Blood Transplantation in Patients with Minimal Residual Disease

Filippo Milano, M.D., Ph.D., Ted Gooley, Ph.D., Brent Wood, M.D.,
Ann Woolfrey, M.D., Mary E. Flowers, M.D., Kristine Doney, M.D.,
Robert Witherspoon, M.D., Marco Mielcarek, M.D., Joachim H. Deeg, M.D.,
Mohamed Sorror, M.D., Ann Dahlberg, M.D., Brenda M. Sandmaier, M.D.,
Rachel Salit, M.D., Effie Petersdorf, M.D., Frederick R. Appelbaum, M.D.,
and Colleen Delaney, M.D.

ABSTRACT

• 582 consecutive pts with acute leukemia or MDS lacking an HLA matched relative receiving a myeloablative transplant from an HLA HLA matched MUD (n=344) or an HLA mismatched MUD (n=98) or an unrelated cord blood donor (n=140).

• Finding: Minimal residual disease status impacted the risk of relapse between the MUD cohorts and the cord blood cohorts.

• Finding: Minimal residual disease status impacted the risk of relapse between the MUD cohorts and the cord blood cohorts

• Among patients with minimal residual disease, the risk of death was higher in the HLA-mismatched group than in the cord-blood group (hazard ratio, 2.92; 95% confidence interval [CI], 1.52 to 5.63; P=0.001); the risk was also higher in the HLA-matched group than in the cord-blood group but not significantly so (hazard ratio, 1.69; 95% CI, 0.94 to 3.02; P=0.08).

Unadjusted Survival and Relapse

Adjusted Survival and Relapse for pts with MRD

**Conclusions:**
- Powerful GVL effects are induced following cord blood transplantation for AML/MDS.
- This effect appears to decrease the risk of relapse compared to recipients of MUD transplants.
- This effect is most pronounced in pts transplanted with MRD, where the reduced risk of relapse was very pronounced and may lead to a survival advantage compared to MUD transplants.

Haploidentical BM Transplants

• Transplants that utilize stem cells collected from a relative who only matches for half of the HLA tissue antigens

• **Advantages:**
  Virtually every patient will have a haplo-identical relative to serve as a stem cell donor

• **Disadvantages:**
  - Higher incidence of graft versus host disease
  - Obligates use of T-cell depleted transplants
  - T-cell depletion increases the risk of
    - graft rejection
    - infection
    - disease relapse.
Post Transplant Cyclophosphamide Following T-cell Replete Haploidentical Transplantation of BM or PBSC
271 patients hematological malignancies – Transplanted single center 2005-2010

- 53 Haploidentical donors
- 117 MRDs
- 101 MUDs

Grade II-IV GVHD

NRM

Relapse

Asad Bashley, Xu Zhang, Connie A. Sizemore, Karen Marion, Stacey Brown, H. Kent Holland, Lawrence E. Morris, and Scott R. Solomon

Bashley et al; JCO 2013
Haploidentical Transplant With Post-Transplant Cyclophosphamide vs MUD Donors For AML

- CIBMTR study comparing outcomes in patients with AML undergoing allogeneic HCT from an 8/8 MUD vs a haplo-identical donor w/ post transplant cytoxan
  - N= 1245 MUD
  - N=104 haplo

- Pts treated from 2008-2012

- 19 centers performed haplo and 80 centers performed MUDs

- Patient characteristics comparable between groups

- More BM grafts with haplo and more PBSC grafts with MUDs
Haploidentical Transplant With Post-Transplant Cyclophosphamide vs MUD Donors For AML

TRM

Myeloablative Reduced Intensity

Relapse

Myeloablative Reduced Intensity

Table 5. Multivariate analysis (subset): risks of acute and chronic GVHD, nonrelapse mortality, relapse, and OS by donor type

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Myeloablative*</th>
<th>Reduced intensity†</th>
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<tbody>
<tr>
<td>Grade 2-4 acute GVHD</td>
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<tr>
<td>Matched unrelated donor</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Haploidentical donor</td>
<td>0.37 (0.23-0.61)</td>
<td>0.71 (0.44-1.15)</td>
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<tr>
<td></td>
<td>*P = .0001</td>
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<tr>
<td>Grade 3-4 acute GVHD</td>
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<tr>
<td>Matched unrelated donor</td>
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<td>1.00</td>
</tr>
<tr>
<td>Haploidentical donor</td>
<td>0.33 (0.14-0.81)</td>
<td>0.21 (0.05-0.86)</td>
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<tr>
<td></td>
<td>*P = .02</td>
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<tr>
<td>Chronic GVHD</td>
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<tr>
<td>Matched unrelated donor</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Haploidentical donor</td>
<td>0.44 (0.29-0.66)</td>
<td>0.45 (0.28-0.71)</td>
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<tr>
<td></td>
<td>*P = .0001</td>
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<tr>
<td>Nonrelapse mortality</td>
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<tr>
<td>Matched unrelated donor</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Haploidentical donor</td>
<td>0.93 (0.54-1.61)</td>
<td>0.59 (0.27-1.29)</td>
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<td>*P = .83</td>
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<tr>
<td>Relapse</td>
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<tr>
<td>Matched unrelated donor</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Haploidentical donor</td>
<td>1.28 (0.911-1.81)</td>
<td>1.53 (1.08-2.22)</td>
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<tr>
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<td>*P = .16</td>
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<tr>
<td>Overall mortality</td>
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<tr>
<td>Matched unrelated donor</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Haploidentical donor</td>
<td>1.19 (0.87-1.61)</td>
<td>1.06 (0.76-1.51)</td>
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<tr>
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<td>*P = .28</td>
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Haploidentical Transplant With Post-Transplant Cyclophosphamide vs MUD Donors For AML

Survival

![Graph showing survival rates for Myeloablative and Reduced Intensity conditioning regimens.](image)

Figure 3. Overall survival. (A) The probability of OS by donor type after myeloablative conditioning regimen, adjusted for age and disease risk index. (B) The probability of OS by donor type after reduced intensity conditioning regimen, adjusted for disease risk index and secondary AML.
Virtually every patient should have a donor stem cell source available to allow an allogeneic transplant, if indicated.
Increasing Use of Unrelated Donor Transplants
U.S. Transplant Activity 1980-2014
Hypothesis: What Transplant Trends May Look Like in 10 years

Richard W. Childs- Speculative Data
Use of Reduced Intensity Conditioning on the Rise

Allogeneic Transplants Registered with the CIBMTR

- Myeloablative
- Non-myeloablative

Number of Transplants

Year: 2002 to 2012

- 2002: Myeloablative 6000, Non-myeloablative 4000
- 2012: Myeloablative 58%, Non-myeloablative 42%

by Conditioning Regimen Intensity
Transplants Being Performed in Increasing Numbers of Older Patients Due to Improving Safety

Trends in Allogeneic Transplants by Recipient Age*

* Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma
Myeloablative vs Reduced Intensity Conditioning For Different Diseases Registered with CIBMTR, 1998-2010
- by Year of Transplant & Disease -
RIC: Decreases Risk Of TRM But May Increase Risk of Relapse For Some Malignancies

Possibility of increased risk of relapse (i.e. myeloma, MDS) with reduced intensity transplants
RIC vs Myeloablative Conditioning (MAC) for MDS or AML in CR: A Phase III Randomized, Multi-Center Study of Allogeneic SCT:

CTN Phase III randomized trial to compare outcomes by conditioning intensity in patients with MDS (N=54) or AML (N=218) in remission.

- The primary endpoint of the study was 18 month overall survival (OS).
- Accrual was stopped early due to a presumed benefit of MAC as assessed by an independent DSMB safety review - decreased relapse.
- Survival better by 7% in the MAC group (p=0.07)

n=272 enrolled
n=135 MAC
n=137 RIC

Conclusion: Because RIC results in higher relapse rates, the data from this trial support MAC as the standard of care for patients able to receive it.

ASH 2015 BMT CTN 0901. B. Scott, et al.
Peripheral Blood Stem Cell Transplants remain the Preferred Graft Cell Source for Allogeneic Transplants

**Pros of PBSCs:**
1. Easy to collect
2. Higher CD34+ Cell dose
3. Lower graft rejection rate

**Cons of PBSCs**
1. Higher cGVHD risk
Chronic GVHD

- Extensive chronic GVHD 32% BM vs 48% PBSC (p=0.001)
- At 2yrs, 57% of BM recipients were off all immunosuppressive therapy vs only 37% of PBSC pts (p=0.026)

Anasetti et al; NEJM 2012: 367:1487
Eligibility Status of Candidates for An Allogeneic Transplant Is In Continuous Flux

**Expanding:**
1. Donor availability not limiting (MUDS, Cords, Haplos)
2. Older patient age (up to 75 years with RIC)
3. Pts with medical co-morbidity eligible

**Contracting:**
1. Some disease categories shrinking as breakthrough drugs developed
   a. CML effectively treated with TKI
   b. High-risk CLL effectively treated with BTK/PI3K inhibitors
   c. Eculizumab for PNH
   d. Immunotherapy breakthrough's (CAR CD19 T-cells)
**Allogeneic HCT for AML in CR1 Decreases Relapse Risk and Improves Survival for Select Patients**

**Methods Cont:**
- 2 cohorts of AML pts (n=185) in CR1 compared based on whether they went to conventional consolidation vs allogeneic HCT
  - All pts < 60 with AML in CR1
  - Pts matched for AML subtype, cytogenetic risk, Age

**Results:**
- Survival at 7 years superior for allo-group compared to conventional consolidation (58\% vs 46\% (p=0.037).
- Relapse lower for allo-group

Stelljes et al JCO 2014:32(4)
Improved Outcome with Allo-HCT for AML Pts in CR1 with Int. and High-risk Cytogenetics
Allogeneic Transplant For AML in CR1 Decreases Relapse Risk and Improves Survival for Select Patients

Results:
- Outcomes superior for older pts with allogeneic HCT

Stelljes et al JCO 2014:32(4)
Causes of Death After Autologous vs Allogeneic Transplants

Causes of Death after Autologous Transplants done in 2011-2012

- Primary Disease: 69%
- Infection: 20%
- Organ Failure: 3%
- Second Malignancy: 7%
- Other: 1%

Causes of Death after HLA Match Sibling Transplants done in 2011-2012

- Primary Disease: 48%
- GVHD: 16%
- Infection: 13%
- Organ Failure: 18%
- Second Malignancy: 4%
- Other: 1%
Transplants Safer- Relapse now is the primary cause of treatment failure after allogeneic HCT

- 10-60% of patients experience relapse post-HCT. (NCI Relapse workshop)

- Majority of relapse occurs by 1 year post-HCT. (Bajwa R, BMT 2012)

Causes of Death after HCT (matched sibling)

- Primary Disease (47%)
- GVHD (14%)
- Infection (12%)
- Other (21%)
- Organ Failure (4%)
- New Malignancy (1%)

CIBMTR Summary Slides, 2011
Outcomes after Post-transplant Relapse are Poor

- 2-year overall survival (OS) in adults with post-transplant relapse:
  - 16% in acute lymphoblastic leukemia (ALL)
  - 14% in acute myelogenous leukemia (AML)

Novel Strategies for Treatment of Post-Transplant Relapse

- **Preemptive therapy upon detection of post transplant MRD**
  - Donor lymphocyte infusion
  - Abrupt withdrawal of CSA or tacro
  - Immuno-modulatory agents
    - 5- Azacytidine
    - Interferon alpha
    - Ipilimumab
    - PD-1 blockade

- **Targeted Immune based Therapies**
  - Vaccination Strategies
  - Donor Leukemia specific T-cells-
  - CAR T-cells (CD19 CAR for relapsed ALL)
Allogeneic T Cells That Express an Anti-CD19 Chimeric Antigen Receptor Induce Remissions of B-Cell Malignancies That Progress After Allogeneic Hematopoietic Stem-Cell Transplantation Without Causing Graft-Versus-Host Disease

- Clinical trial of allogeneic T cells genetically engineered to express a chimeric antigen receptor (CAR) targeting the B-cell antigen CD19 for patients with B-cell malignancies that had progressed after allo-HSCT.
- Pts received a single infusion of CAR T cells. No chemotherapy or other therapies were administered. The T cells were obtained from each recipient's alloHSCT donor.

Brudno et al JCO 2016
Allogeneic T Cells That Express an Anti-CD19 Chimeric Antigen Receptor Induce Remissions of B-Cell Malignancies That Progress After Allogeneic Hematopoietic Stem-Cell Transplantation Without Causing Graft-Versus-Host Disease

- 8/20 achieved a response including 6 CRs and 2 PRs.
  - Response rate highest for ALL (4/5 MRD negative CR)
  - No patients developed GVHD

Brudno et al JCO 2016
Donor CD19 CAR T cells exert potent graft-versus-lymphoma activity with diminished graft-versus-host activity

- Mouse modal of lymphoma in which allogeneic CD19 CAR T-cells were adoptively transferred into lymphoma bearing mice.
- T-cells with the CD19 CAR that were alloreactive experienced enhanced stimulation and were rapidly deleted or exhausted before they could cause GVHD.
- In contrast, non alloreactive CD19 CAR T cells persisted and mediated anti-lymphoma activity.
- These data show that concomitant engagement of the native T-cell receptor and the CAR leads to T-cell exhaustion/deletion preventing alloreactive CAR T0-cells from causing GVHD.

Ghosh et al Nature Medicine 2017
Targeting the CTLA4/PD-1 pathway in patients with relapsed dz following allogeneic stem cell transplant

• **Pros**
  - Can reactivate Allogeneic T-cells that contribute to graft-vs-tumor effect
  - Disease regression including CRs described when given post allogeneic transplant

• **Cons**
  - Can reactivate Allogeneic T-cells that cause GVHD
    • Death from GVHD following nivolumab reported
  - Not an option for patients with active or recent GVHD
The Future of Allogeneic BMT

• **Success of haplo-transplants:**
  - Will lead to more annual transplants world-wide

• **Reduced mortality of allotransplants**
  - Transplants performed earlier in disease course- (i.e AML)- will reduce risk of disease relapse

• **More routine use of cellular therapy to improve transplant outcomes**
  - Viral reactive T-cells (allogeneic/frozen/ partially HLA-matched off the shelf

• **Grafts engineered to improve transplant outcomes will gain increasing use**
  - (i.e. partial T-cell depleted PBSC transplants, CD34 selected transplants)