Hematopoietic Stem Cell Transplantation: Current Status and Future Directions

RICHARD W. CHILDS M.D.
NIH, BETHESDA MD
**Stem cell transplantation**

**Autologous**

- **Autologous stem cell collection**
- **Conditioning regimen**
- **Freeze Stem Cells**
- **Thaw + transplant**

**First-Line Therapy:**
- Multiple Myeloma
  - Prolongs PFS and survival (Attal et al-NEJM-1996)

**Second-Line Therapy:**
- Relapsed Hodgkin's and NHL
  - Prolongs survival in NHL (Parma Trial-1995)
  - Prolongs DFS in HDz (but not survival)
**Stem cell transplantation**

**Autologous**

- Patient
- Autologous stem cell collection
- Freezing Stem Cells
- Conditioning regimen
- Thaw + transplant

**Allogeneic**

- Patient
- Stem cell donor
- Allogeneic stem cell collection
- Conditioning regimen
- Transplant

Tissue or HLA matched
Stem Cells Source

**Peripheral Blood**

G-CSF subcutaneous injection for 5 days. Mononuclear cells collected by apheresis

**Bone Marrow**

Direct aspiration under general

**Umbilical Cord Blood**

Placental blood directly drained into bag
How Does Myeloablative Allogeneic BMT Cure?

Pre-transplant intensive therapy

1) Conditioning Regimen

Leukemia cells

Transplant Day 0

2) Graft-vs-Tumor

Allograft (PBSC + Lymphs)

Remission

GVL

T-Cells
Types of Allogeneic Transplants

• *Conventional High Dose or Myeloablative Transplant*
  – Conditioning fully eradicates the host's bone marrow

• *Reduced Intensity Conditioning (RIC)*
  – Low dose or non-myeloablative transplant
  – Immunologically eradicates host bone marrow
Use of Reduced Intensity Conditioning on the Rise

Allogeneic Transplants Registered with the CIBMTR

- Myeloablative
- Non-myeloablative

Number of Transplants


Myeloablative: 58%
Non-myeloablative: 42%

CIBMTR
Center for International Blood & Marrow Transplant Research

by Conditioning Regimen Intensity
Allogeneic Hematopoietic Stem Cell Transplantation: Can Cure Patients With Chemotherapy Refractory Hematological Malignancies
Graft-vs-Tumor Effects After Reduced Intensity Allogeneic Hematopoietic Cell Transplantation Can Cure
T-cell Mediated Graft-Vs-Leukemia Effects Can Cure Chemotherapy Resistant Malignancies

May 2006
1 month
After transplant

NHLBI Hematology Branch Transplant Protocol 02-H-0250
Hematological Malignancies Vary in Their Susceptibility To Graft-Vs-Leukemia (GVL) Effects

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Susceptibility to GVL (response to DLI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML chronic phase</td>
<td>High</td>
</tr>
<tr>
<td>CLL</td>
<td>High</td>
</tr>
<tr>
<td>Low-grade NHL</td>
<td>High</td>
</tr>
<tr>
<td>AML/ALL</td>
<td>Intermediate</td>
</tr>
<tr>
<td>MDS</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Intermediate/low</td>
</tr>
<tr>
<td>Int/high grade NHL</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Refractory ALL/AML</td>
<td>Low</td>
</tr>
<tr>
<td>CML blast crisis</td>
<td>Low</td>
</tr>
</tbody>
</table>
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
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)
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
REQUIREMENTS FOR ALLOGENEIC TRANSPLANTATION

- An HLA compatible donor to donate stem cells
  - 25% each sibling will be HLA identical
  - In the U.S., there is approximately a 25% that a patients will have an HLA identical sibling
Finding An Unrelated HLA Identical Donor.....
A 1/10,000 chance

20 million donors in the World-Wide Registry=60% chance

NMDP=National Marrow Donor Program
Based on Current Donor Availability and with Recruitment Trends Extended to 2017.

- Unrelated donors now more than 20 million volunteers world-wide registered
- Age cut-off 60 years
## Availability of a Stem Cell Sources for Allogeneic Transplantation

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

Chances of Finding a Stem Cell Donor

Potential Candidates For a Cord Blood Transplant or A Haploidentical Transplant
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

60-80% of patients will have a cord unit in the public registry that could be used for a transplant.

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
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 depletion
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 Sorrer, 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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cord-Blood Group (N = 140)</th>
<th>HLA-Matched Group (N = 344)</th>
<th>HLA-Mismatched Group (N = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age†—yrs</td>
<td>29</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>Weight—kg†</td>
<td>70</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>Female sex—no. (%)</td>
<td>68 (49)</td>
<td>150 (46)</td>
<td>45 (46)</td>
</tr>
<tr>
<td>Race—no. (%)†</td>
<td>64 (46)</td>
<td>294 (85)</td>
<td>76 (78)</td>
</tr>
<tr>
<td>Positive serostatus for cytomegalovirus—no. (%)</td>
<td>86 (61)</td>
<td>178 (52)</td>
<td>47 (48)</td>
</tr>
<tr>
<td>Diagnosis—no. (%)</td>
<td>73 (52)</td>
<td>175 (51)</td>
<td>52 (53)</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute lymphoid leukemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease risk—no. (%)†</td>
<td>93 (66)</td>
<td>276 (80)</td>
<td>77 (79)</td>
</tr>
<tr>
<td>Low or intermediate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High or very high</td>
<td>47 (34)</td>
<td>68 (20)</td>
<td>21 (21)</td>
</tr>
<tr>
<td>Conditioning regimen—no. (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludarabine, cyclophosphamide, and total-body irradiation at a dose of 1320 cGy</td>
<td>97 (69)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treosulfan, fludarabine, and total-body irradiation at a dose of 200 cGy</td>
<td>43 (31)</td>
<td>64 (19)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Busulfan with either cyclophosphamide or fludarabine</td>
<td>0</td>
<td>127 (37)</td>
<td>54 (55)</td>
</tr>
<tr>
<td>Cyclophosphamide and total body irradiation at a dose of 1200 or 1320 cGy</td>
<td>0</td>
<td>153 (44)</td>
<td>37 (38)</td>
</tr>
<tr>
<td>GVHD prophylaxis—no. (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine and mycophenolate mofetil</td>
<td>140 (100)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tacrolimus and methotrexate</td>
<td>—</td>
<td>268 (78)</td>
<td>98 (100)</td>
</tr>
<tr>
<td>Other</td>
<td>76 (22)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Presence of minimal residual disease—no./total no. (%)</td>
<td>45/137 (33)</td>
<td>104/331 (33)</td>
<td>35/90 (39)</td>
</tr>
</tbody>
</table>

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).

Table 2. Adjusted Cox Regression Models for Analyses of Death and Relapse, According to Minimal Residual Disease Status.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without minimal residual disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord-blood group</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>HLA-matched group</td>
<td>0.78 (0.48–1.28)</td>
<td>0.33</td>
</tr>
<tr>
<td>HLA-mismatched group</td>
<td>1.36 (0.76–2.46)</td>
<td>0.30</td>
</tr>
<tr>
<td>Patients with minimal residual disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord-blood group</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>HLA-matched group</td>
<td>1.69 (0.94–3.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>HLA-mismatched group</td>
<td>2.92 (1.52–5.63)</td>
<td>0.001</td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without minimal residual disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord-blood group</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>HLA-matched group</td>
<td>1.30 (0.65–2.58)</td>
<td>0.46</td>
</tr>
<tr>
<td>HLA-mismatched group</td>
<td>1.28 (0.51–3.25)</td>
<td>0.60</td>
</tr>
<tr>
<td>Patients with minimal residual disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord-blood group</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>HLA-matched group</td>
<td>2.92 (1.34–6.35)</td>
<td>0.007</td>
</tr>
<tr>
<td>HLA-mismatched group</td>
<td>3.01 (1.22–7.38)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Unadjusted Survival and Relapse

Figure 1. Unadjusted and Adjusted Estimates of Overall 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.

Post Transplant Cyclophosphamide Following T-cell Replete Haploidentical Transplantation of BM or PBSC

Fuchs E. et al JHU
Haploidentical Transplant With Post-Transplant Cyclophosphamide has similar outcome to matched unrelated transplants

Survival

![Diagram 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.
Increasing Use of Unrelated Donor Transplants
U.S. Transplant Activity 1980-2014
Hypothesis: What Transplant Trends May Look Like in 10 years
Virtually every patient should have a donor stem cell source available to allow an allogeneic transplant, if indicated.

In the year 2017
Complications of an Allogeneic Stem Cell Transplant

1. Toxicities related to the conditioning regimen
   - Mucosal inflammation (Mucositis)
   - Liver toxicity (Veno-occlusive disease)
   - Lung inflammation (pneumonitis)

2. Graft Rejection
   - occurs rarely with conventional transplants

3. Infection
   - bacterial/fungal: during neutropenic phase of transplant
   - Viral: first 100 days of the transplant

4. Graft vs host disease - decreases relapse risk
   - acute: from engraftment until day +100
   - Chronic: from day 100 until 2 years post transplant

5. Drug toxicities
   - many drugs given to prevent infection/GVHD have toxicities
Mortality is Decreasing with Allogeneic Stem Cell Transplants

- 60% reduction in TRM
- N = 1418
- N = 1148
- Bacterial, viral and fungal infections reduced
- Reduction in severe Grade III-IV GVHD
- Dramatic reduction in day 200 transplant-related mortality (TRM) and overall TRM

Gooley et al; NEJM 2010: 363;22
Improving transplant outcome

One-Year Survival, percent

- HLA-matched sibling
- URD

Better supportive care
Gentler conditioning
Improved mgmt of GVHD

Pasquini MC, Wang Z. CIBMTR
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)
Am I a Candidate for an Allogeneic Stem Cell Transplant?
Questions To Be Answered

• Does the potential benefit of a transplant justify the risk?
  (i.e. do I have a disease that chemotherapy can cure or make me live a long time or a disease where chemotherapy is unlikely to cure in contrast to a transplant that has a higher probability of cure)

• Is my disease controlled sufficiently to where a transplant would help?
  i.e. Acute leukemias should be in remission before transplant

• Do I Have a stem cell donor?
  • HLA tissue matched sibling
  • Matched Unrelated donor
  • Cord blood or haplo-identical donor

• What are the chances I could be harmed by a transplant?
  • Am I Healthy enough to go through the procedure?
  • Am I young enough?
  • Have prior treatments put me at increased risk for complications
Long-term Survival after HCT

- CIBMTR study of 10,632 allogeneic HCT recipients surviving ≥ 2 years in remission (median follow-up 9 years)

J Wingard et al, J Clin Oncol. 2011 Jun 1;29(16):2230-9
TWENTY YEARS of ALLOGENEIC STEM CELL TRANSPLANTATION at NIH

SCIENTIFIC DAY
THURSDAY, SEPTEMBER 11, 2014
8:00 a.m. — 5:00 p.m.

MASUR AUDITORIUM, BUILDING 10
Bethesda, MD

Program details and registration for either or both days at:

SURVIVORSHIP DAY
FRIDAY, SEPTEMBER 12, 2014
12:00 p.m. — 4:00 p.m.
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)
Clinical Research Focus in Hematology

- Aplastic Anemia and bone marrow failure syndromes
- CLL
- AML
- Sickle Cell Anemia
- Gene therapy for Sickle Cell anemia
- Allogeneic stem cell transplantation
  - Aplastic anemia/BMFS
  - Hematological Malignancies
  - Sickle Cell Anemia