Adult Stem Cell Transplant and Treatment of Blood Cancers

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Dr. Saral at Johns Hopkins ~ 1974
1949: Surviving Lethal Radiation by Lead-Shielding of Spleen


**Marrow**

- B lymphocytes
- Lymphoid stem cells
- Pluripotent stem cell
- Myeloid stem cells
- T lymphocytes

**Blood**

- Red blood cells
- Platelets
- Monocytes
- Neutrophils
- Eosinophils
- Basophils

1956
Principle of Marrow Grafting

- High-Dose Chemo-Radiation Therapy
  - Destroys diseased marrow
  - Suppresses patient’s immune cells so that marrow graft will be accepted

- Healthy Marrow Graft
  - Replaces diseased marrow

Bone Marrow Harvest

PBSC Collection
## Human Marrow Grafts 1958-67

<table>
<thead>
<tr>
<th>Diseases</th>
<th># Patients</th>
<th>Total</th>
<th>Graft Failure</th>
<th>GVHD</th>
<th>Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic anemia</td>
<td>73</td>
<td>66</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>115</td>
<td>56</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immunodeficiencies</td>
<td>12</td>
<td>3</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>200</strong></td>
<td><strong>125</strong></td>
<td><strong>47</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
</tr>
</tbody>
</table>


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## Mouse ≠ Large Mammals

"Many errors in extrapolation from the laboratory experiment to the patient have been made and much time was lost before it became evident that the GVH reaction in primates (random-bred large animals) including man is incomparably more violent than in (inbred) rodents."

van Bekkum, 1967

Seattle Team in 1965

Rainer Storb  Bob Epstein  Dean Buckner

Don Thomas

Our Letterhead

Division of Hematology and Transportation
Unresolved Issues in 1965

- Conditioning regimen
- Role of histocompatibility
- GVHD prevention
- Sources of stem cells

Histocompatibility Typing Mid-Late 1960s

**Humans**
- Dausset: MAC; v. Rood: 4a + b
  - Sera from parous women + transfusion recipients
- Bach: MLC

**Dogs**
- Seattle: groups a–h and MLC
  - Sera from cross-immunized littermates

Tests: Leukoagglutination or lymphocytotoxicity (trypan blue exclusion)
Leukocyte Agglutination Test
Dausset’s Method

Negative Reaction
Weakly Positive Reaction
Positive Reaction

+++ Positive Reaction
++++ Positive Reaction
+++++ Positive Reaction


1140 cGy TBI + Littermate Marrow

WBC x 10^3
0 5 10 15 20 25 30

DLA Matched (n=6)

WBC x 10^3
0 2 4 6 8 10 12 14

DLA Mismatched (n=6)

Not Anticipated From Murine Studies

Acute, Fatal GVHD in MHC-identical Dogs

Importance of Minor Antigens

Post-transplant Immunosuppression
1968 Canine Long-Term Survivors

Patient with 1° Refractory AML

Storb et al., Blood 44: 57, 1974
Immunosuppression

DLA-Nonidentical Unrelated Dogs (9.2 Gy TBI)

% Survival

Days After Marrow Graft

MTX + CSP (N=17)

Long MTX (N=75)

CSP (N=15)

No Immunosuppression (N=64)

Deeg et al. Transplantation 34: 30-5, 1982

Immunosuppression

Aplastic Anemia
Cy

Years after Sibling HCT

MTX + CSP (n=22)

MTX (n=24)

.72

.38

Storb et al., Blood 68:119, 1986
(updated in Sorror et al, BBMT 2005)

CML
Cy / TBI

CSP/MTX (n=26)

CSP (n=29)

1986

Storb et al., NEJM 314:729, 1986
(updated in Sorror et al, BBMT 2005)
BU/CY Regimen in AML

Survival of Dogs Conditioned with 9.2 Gy and Given DLA-nonidentical HCT

Storb, et al., Transplantation 56: 800, 1993
PBSC vs. Marrow for Malignancies

- **High-risk Malignancies**
- **Standard-risk Malignancies**

Years after HLA-id. Sibling HCT

Bensinger et al., NEJM 344: 175, 2001
Melcarek et al., Blood 119, 2675, 2012
Supportive Care Advances

- Bactrim for pneumocystis jiroveci
- Acyclovir for HSV and VZV
- CMV monitoring / ganciclovir prophylaxis
- Fluconazole prophylaxis
- New antifungals and antibiotics

Novel Allogeneic HCT Approach

- Substitute nonmyeloablative conditioning for toxic high-dose chemoradiotherapy
- Use novel postgrafting immunosuppression to both prevent graft rejection and control GVHD
- Grafted immune cells eliminate cancer*

Patients with advanced hematologic malignancies
- Older
- With comorbidities
- Failed high-intensity HCT

Clinical Treatment Protocol
- FLU 30 mg/m²/d
- CSP 5 mg/kg po BID
- MMF 15 mg/kg po BID / TID
- 2 Gy TBI G-PBMC
- Chimerism Analyses
"Isolation" in 2001

First 1,092 Pts. with Advanced Heme Malignancies (median age 56 [7-75] yrs)

Relapse Mortality

- Relapse Rate: Related 45%
- Unrelated 42%
- Relapse Mortality 34.5%

Non-Relapse Mortality

- NRM 24%

FHCRC unpubl.
Storb et al., JCO, in press
% Survival

Years After Transplantation

Storb et al., J Clin Oncol, in press (as of 10-01-2012).

α- versus β-emitters

α-particle
Range: 40-90 μM
LET 100 keV/μM
\( t_{1/2} \): 211At 7.2 hrs
213Bi 46 min

Favorable properties of α-emitters
Short path length
High linear energy transfer (LET)
Short half-life

β-particle
Range: 800-5000 μM
LET 0.8 keV/μM
\( t_{1/2} \): 90Y 2.5 day
131I 8.1 day

Storb Emory Talk_2014.ppt
Alternatives for Patients Without HLA-Matched Donors

- HLA-haploidentical related grafts
- Unrelated cord blood transplantation

1988 Reunion of Long-Term Surviving Patients