The Atomic Bomb Approach to Medicine

- Little Boy bomb dropped on Hiroshima August 6, 1945
- 90-166,000 deaths
- 15-20% death from radiation sickness characterized by anemia, leukopenia, thrombocytopenia, gastrointestinal, and neurologic disturbances
Early Animal Studies

• Spleen shielding rescued otherwise lethally irradiated mice. (Jacobson et al 1949)

• Bone marrow injection rescued otherwise lethally irradiated mice and guinea pigs. (Lorenz et al 1951)

• Secondary disease – A mortal wasting syndrome of skin abnormalities and diarrhea occurring in allogeneically transplanted mice (Barnes & Loutit 1955).

• Methotrexate increased survival and attenuated secondary disease (Uphoff 1958)
E. Donnall Thomas, MD
(1920 – 2012)

1990 Nobel Prize in Medicine or Physiology with Joseph Murray
Intravenous Infusion of Bone Marrow In Patients Receiving Radiation and Chemotherapy

• Six terminal patients
• Variety of graft sources and doses: fetal and adult marrow from long bones and ribs
• Short lived engraftment of donor cells in 2 out of 6 patients only.
• Not very promising.

Goals for Today

• What are the most common indications for HCT?
• How is HCT done?
• How do various components affect the outcome?
Terminology

- Bone marrow transplant
- Hematopoietic stem cell transplant
- Hematopoietic progenitor cell transplant
- Peripheral blood stem cell transplant

The transfer of hematopoietic progenitor cells for therapeutic purposes
Basic Definitions

• Autologous HCT – A transplant using a patient’s own cells for the graft.
• Allogeneic HCT – A transplant using another person’s cells for the graft.
Diseases with well defined indications for transplant

• Autologous transplants
  – Multiple myeloma
  – Relapsed diffuse large B cell lymphoma
  – Relapsed germ cell tumors

• Allogeneic transplants
  – Intermediate to high risk acute leukemia
  – Intermediate to high risk myelodysplastic syndrome
  – Severe aplastic anemia
Purpose of Transplant

• To replace hematopoiesis
• To modulate the immune response
• Donor source reflects purpose
Autologous HCT

- Patient
  - Regular Chemo ± XRT
  - Blood or Marrow Collection
  - High dose Chemo ± XRT
  - 8-14 days
- Freezer
  - 8-14 days
Indications for autoHCT

- Diseases in which cytoreduction (by chemotherapy) is effective and dose dependent
  - Germ cell tumors (testicular)
  - Large cell lymphoma
  - Myeloma
- Replacement of hematopoiesis
- Rescue therapy
Indications for alloHCT

• Replacement of hematopoiesis
• Immune mediated effect against the underlying malignancy (graft versus tumor effect)
• Prevention of relapse
Allogeneic HCT

Patient

Donor

Regular Chemo ± XRT

High dose Chemo ± XRT

14-21 days

Time
Indications for allo HCT

• Immune mediated effects
  – Acute leukemia
  – Myelodysplastic syndrome

• Replacement of damaged bone marrow / hematopoiesis
  – Aplastic anemia
Allogeneic BMT Survival Outcomes (AML)

- Acute GvHD (15%)
- Infection (10%)
- Other (5%)
- Chronic GvHD, dead (15%)
- Disease relapse (20%)
- Chronic GvHD, alive (15%)
- Alive and well (20%)
A transplant is a bet against the future

Leukemia Therapy

High dose Chemo ± XRT

35%

65%

5%

95%
Genetic Subgroup Analysis: RFS

**NPM1+/FLT3 ITD-**

- **donor** n=35
- **no donor** n=92

- **p=0.71**

**Others**

- **donor** n=45
- **no donor** n=125

- **p=0.02**

*Courtesy of Schlenk R et al, NEJM 2008*
MUD Transplantation in Relapsed Patients with Unfavorable Genotype

- Other strategy: n=67
- MUD: n=37

Survival after relapse (%)

$p<0.0001$

- MUD: n=37
- Other strategy: n=67

Time (months)
## Donor source reflects purpose

<table>
<thead>
<tr>
<th></th>
<th>Hematopoietic rescue</th>
<th>Immune therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autologous</strong></td>
<td>XXX</td>
<td>X</td>
</tr>
<tr>
<td><strong>Allogeneic</strong></td>
<td>XXX</td>
<td>XXX</td>
</tr>
</tbody>
</table>
Immune Cell Populations Before AutoHCT for Myeloma

Hahn, et al. ASH 2013
Adjusted probabilities of leukemia-free survival rates after identical twin bone marrow transplantations with high (more than $3 \times 10^8$ cells/kg) versus low (less than or equal to $3 \times 10^8$ cells/kg) cell doses.


©2000 by American Society of Hematology
HOW
Autologous HCT

Patient

Regular Chemo ± XRT

Blood or Marrow Collection

Freezer

High dose Chemo ± XRT

8-14 days
Allogeneic BMT

- Regular Chemo ± XRT
- High dose Chemo ± XRT

14-21 days

Time
• Donor selection
• Conditioning regimens
• Complications
  – Acute graft versus host disease
  – Chronic graft versus host disease
• Graft failure/chimerism
Donor Selection

- Human leukocyte antigen (HLA) matching
- Relatedness
- Cytomegalovirus status
- Age
- Gender (parity)
HLA

• On surface of most body cells
• The most important proteins in transplant
• Normal function is to present antigen to T cells.
• Responsible for graft rejection and GvHD
HLA

<table>
<thead>
<tr>
<th>HLA</th>
<th>DRB1</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>DQB1</th>
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</thead>
<tbody>
<tr>
<td>Alleles</td>
<td>400</td>
<td>370</td>
<td>660</td>
<td>190</td>
<td>62</td>
</tr>
</tbody>
</table>

- \((>1 \times 10^{12} \text{ haplotypes})^2 = > 1 \times 10^{24} \text{ combinations}\)
- Not all alleles have been identified
- Frequencies are not equally distributed
Chance of a matched sibling $= 1 - 0.75 \# \text{ of siblings}$
## HLA

<table>
<thead>
<tr>
<th>Donor</th>
<th>Maternal Haplotype</th>
<th>Paternal Haplotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DR</td>
<td>B</td>
</tr>
<tr>
<td>MUD</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MRD</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Haplo</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
• Donor selection
• Conditioning regimens
• Complications
  – Acute graft versus host disease
  – Chronic graft versus host disease
• Graft failure/chimerism
• Donor selection
• Conditioning regimens
• Complications
  – Acute graft versus host disease
  – Chronic graft versus host disease
• Graft failure/chimerism
Allogeneic BMT

Patient

Regular Chemo ± XRT

Donor

High dose Chemo ± XRT

14-21 days

Time
Transplant regimens

- **Flu-Cy**
- **Flu-Cy-ATG**
- **Flu-low dose TBI**
- **Flu ATG**
- **TLI/ATG**
- **FLU/CY/TBI 200 cGy**

- **Cy-TBI 1200 cGY**
- **Bu-Cy**
- **Mel 200**

- **Regimen Related Toxicity**

- **Later Graft-versus Disease Effect**
- **Earlier Anti-Disease Effect**

- **Relapse**

- **Myelosuppression**
Reduced Intensity AlloBMT
A transplant is a bet against the future

Leukemia Therapy

High dose Chemo ± XRT

35%

65%

5%

95%
• Donor selection
• Conditioning regimens
• Complications
  – Acute graft versus host disease
  – Chronic graft versus host disease
• Graft failure/chimerism
Leukemia

BMT

GVHD
Immunologic Effects of Allogeneic Grafts

- Graft-versus-Tumor Effects – Reaction of the donor immune system against the recipient’s malignancy
- Graft-versus-Host Effects – Reaction of the donor immune system against the recipient’s body tissues.
- Different sides of the same coin.
Probability of Relapse After 2,254 HLA-identical Sibling Transplants for Early Leukemia

- Twins (N=70)
- T Cell Depletion (n=401)
- No GVHD (n=433)
- AGVHD Only (n=738)
- CGVHD Only (N=127)
- AGVHD + CGVHD (N=485)
Billingham Criteria (1966)

- The graft must contain immunologically competent cells.
- The host must possess important transplantation alloantigens that are lacking in the donor graft, so that the host appears foreign to the graft, and is, therefore, capable of stimulating it antigenically.
- The host itself must be incapable of mounting an effective immunological reaction against the graft, at least for sufficient time for the latter to manifest its immunological capabilities; that is, it (the graft) must have the security of tenure.
Acute Graft-versus-Host Disease

• Reaction of donor’s immune system against the recipient’s body tissues
• Manifests as diarrhea, skin rash, liver test abnormalities usually within the first 100 days.
• ~20-50% of allogeneic transplants will develop some aGvHD
• Associated with a 15-20% mortality
Acute GvHD Therapy

- **Prophylaxis** – Attempts to prevent aGvHD development
- **Treatment** – For therapy of aGvHD once it occurs
Prophylaxis

• Pharmacologic – Calcineurin inhibitor and methotrexate after transplant
• T cell depletion
  – Ex vivo CD34 selection or T cell depletion of the graft
  – In vivo anti-thymocyte globulin or anti-CD52
• Post transplant high dose cyclophosphamide
## T Cell Depletion vs. Pharmacologic Approaches

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Acute GvHD</th>
<th>Long term</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCD vs. CSA/MTX</td>
<td>48</td>
<td>23% vs. 12%</td>
<td>LFS: 42 vs 44% @ 3 yrs</td>
</tr>
<tr>
<td>Partial TCD/CSA vs. CSA/MTX</td>
<td>400</td>
<td>18% vs. 37%</td>
<td>cGvHD: 18 vs. 37% DFS @ 3 years the same</td>
</tr>
<tr>
<td>TLI/ATG</td>
<td>37</td>
<td>1/37 (3%)</td>
<td>cGvHD: 27% of patients surviving &gt;100d</td>
</tr>
</tbody>
</table>
High dose cyclophosphamide
Post HCT cyclophosphamide (Cy) for GvHD

Day 0

Diagram:

- Cycle 1
- Cycle 2
- Cycle 3
- Cycle 4

Note: The diagram shows cycles labeled as 'C'.
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
**HCT for hematologic malignancy**

<table>
<thead>
<tr>
<th></th>
<th>Haplo*</th>
<th>Standard#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning</td>
<td>Flu/Cy/TBI</td>
<td>Flu/Mel/TBI</td>
</tr>
<tr>
<td>aGvHD prophylaxis</td>
<td>Cy/Tac/MMF</td>
<td>uMTX/Tac/MMF</td>
</tr>
<tr>
<td>Graft failure</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>aGvHD Gr. III-IV</td>
<td>6% (day 200)</td>
<td>27% (day 100)</td>
</tr>
<tr>
<td>Progression free</td>
<td>26% (2 years)</td>
<td>44% (2 years)</td>
</tr>
<tr>
<td>overall survival</td>
<td>36% (2 years)</td>
<td>47% (2 years)</td>
</tr>
</tbody>
</table>

Chronic Graft-versus-Host Disease

• Post transplant complication usually occurring > 100 days characterized by
  – Fibrotic skin disease
  – Dry and gritty mouth eyes due to glandular destruction
  – Gastrointestinal fibrosis with malnutrition

• 50% of long term survivors will develop some form of cGvHD

• Chronic GvHD is the major cause of long term mortality other than relapse after transplant
• Donor selection
• Conditioning regimens
• Complications
  – Acute graft versus host disease
  – Chronic graft versus host disease
• Graft failure/chimerism
KHIMAIRA (Greek) was a three headed, fire-breathing creature with the fore-parts of a lion, the hindquarters of a goat, and the tail of a serpent. The Chimera was slain by Bellerophon astride Pegasus.
Donor Chimerism

- RIC or NMA Rx
- 14-21 days
- Donor lymphocyte infusion
- Remove immunosuppression

Full

Mixed

Time
Graft Failure

• Failure to recover leukocytes, platelets, and erythrocytes by day 28

• Causes
  – Anti-HLA antibodies
  – Viral infections – EBV!
  – Inadequate immunosuppression (host versus graft reactions)
  – Infected grafts
  – Large spleen (in myelofibrosis)

• Autologous recovery can occur.

• Treatment is another transplant