Introduction to Clinical Hematopoietic Cell Transplantation (HCT)

Oncology for Scientists
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Goals for Today

• What is HCT?
• How is HCT done and how is it tailored to fit the patient’s disease and circumstances?
Important Concepts

• Autologous vs allogeneic HCT
• Myeloablative vs reduced intensity conditioning regimens
• Autologous, syngeneic, matched related, matched unrelated, mismatched and haploidentical donors
• Acute vs. chronic graft versus host disease
• Donor chimerism
What is HCT?

The transfer of hematopoietic progenitor and stem cells for therapeutic purposes

• Bone marrow transplant
• Hematopoietic stem cell transplant
• Hematopoietic progenitor cell transplant
• Peripheral blood stem cell transplant
Important Concepts

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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.
Autologous HCT

- Patient
- Autologous HCT
- High dose Chemo ± XRT
- Regular Chemo ± XRT
- Blood or Marrow Collection
- 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)
Allogeneic HCT

Patient

Donor

Regular Chemo ± XRT

High dose Chemo ± XRT

14-21 days

Time

Donor
Indications for alloHCT

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

\[ \text{NPM1+/FLT3 ITD-} \]

\[ \text{Others} \]

\[ p=0.71 \]

\[ \text{donor n=35} \]

\[ \text{no donor n=92} \]

\[ p=0.02 \]

\[ \text{donor n=45} \]

\[ \text{no donor n=125} \]

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

Survival after relapse (%)

0 20 40 60 80 100

0 12 24 36 48 60

MUD n=37

other strategy n=67

p<0.0001
Important Concepts

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Allogeneic BMT

- Patient
  - Regular Chemo ± XRT
  - High dose Chemo ± XRT

- Donor
  - 14-21 days
  - Time
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
Reduced Intensity AlloBMT

Patient

Regular Therapy

Donor

Immunosuppression
± Chemo ± XRT

14-21 days

Time
Transplant regimens

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

- **Allo Reduced Intensity**
  - Flu-Mel
  - Flu-Bu
  - Flu-Mel-TBI 400 cGy

- **Auto and Allo Myeloablative**
  - Cy-TBI 1200 cGY
  - Bu-Cy
  - Mel 200

- **Regimen Related Toxicity**

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

Myelosuppression
Myeloablation

Reduced intensity

Chemo

Months

Chemo

Months

R.I.P.
Cyclophosphamide

Fludarabine

Bu, Mel, TBI
Important Concepts

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• Donor chimerism
Donor source reflects purpose

<table>
<thead>
<tr>
<th></th>
<th>Rescue hematopoiesis</th>
<th>Immune therapy</th>
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<tbody>
<tr>
<td>Autologous</td>
<td>XXX</td>
<td>X</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>XXX</td>
<td>XXX</td>
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</tbody>
</table>
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.

HLA (aka MHC)

- 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

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HLA (aka MHC)

- (>1 * 10^{12} haplotypes)^2 = > 1 * 10^{24} combinations
- Not all alleles have been identified
- Frequencies are not equally distributed

<table>
<thead>
<tr>
<th>HLA</th>
<th>DRB1</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>DQB1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alleles</td>
<td>400</td>
<td>370</td>
<td>660</td>
<td>190</td>
<td>62</td>
</tr>
</tbody>
</table>
Chance of a matched sibling = $1 - 0.75$ # of siblings
# Genetic Differences Between Donors

<table>
<thead>
<tr>
<th>DNR</th>
<th>Maternal Haplotype</th>
<th>Paternal Haplotype</th>
<th>mMHC</th>
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<tbody>
<tr>
<td></td>
<td>DR</td>
<td>B</td>
<td>A</td>
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<tr>
<td>MUD</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MRD</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Haplo</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Synge</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Auto</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Donor Selection

- Human leukocyte antigen (HLA) matching
- Relatedness
- Cytomegalovirus status
- Age
- Gender (parity)
- Not blood ABO type (so far)
Important Concepts

- Autologous vs allogeneic HCT
- Myeloablative vs reduced intensity conditioning regimens
- Autologous, syngeneic, matched related, matched unrelated, mismatched and haploidentical donors
- **Acute vs. chronic graft versus host disease**
- Donor chimerism
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)

Years
Probability of Relapse, %
0 10 20 30 40 50 60 70 80 90 100
0 1 2 3 4 5 6
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 GvHD

- 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%</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

Day
-6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8

FLU-CY-TBI

CY

TAC and MMF
High dose cyclophosphamide

Day -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8

TAC and MMF

FLU-CY-TBI

Patient

Regular Therapy

Donor

14-21 d

Time

CY
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
Post HCT cyclophosphamide (Cy) for GvHD
# HCT for hematologic malignancy

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

Something to think about

- How does Billingham’s hypothesis explain how post-transplant cyclophosphamide prevents acute graft-versus-host disease?
- What property does cyclophosphamide have that enables its use after transplant without endangering the graft?
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
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KHIMAIIRA (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.

http://www.theoi.com/Tartaros/Khimaira.html
Donor Chimerism

- RIC or NMA Rx
- 14-21 days
- Full
- Mixed
- Time
- Remove immuno-suppression
- Donor lymphocyte infusion

Donor lymphocyte infusion