Challenges of Hematopoietic Stem Cell Transplantation

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Hematopoietic Stem Cell Transplantation

Objectives

- Deliver sufficient chemo-radio therapy to destroy tumor cells (old paradigm)
- Provide a source of hematopoietic stem cells to replace ablated marrow of patient
- Establish organ graft tolerance to prevent rejection of donor cells
- Provide immune effector cells to mediate graft-vs-tumor activity
Indications for Stem Cell Transplantation

- Benefit documented by randomized trials
  - intermediate grade NHL, sensitive relapse
  - multiple myeloma
  - High risk first remission acute leukemia
- Curative potential, benefit inferred
  - AML/ALL beyond CR1
  - CML
  - MDS
  - Aplastic anemia, congenital immune deficiencies
  - low grade lymphoma/CLL
  - hemoglobinopathies
- Benefit not yet established
  - Solid tumors, autoimmune disease, regenerative medicine
Obstacles to Success

• Finding a compatible donor
• Limiting transplant related complications
• Preventing disease relapse
Hematopoietic Stem Cells

- **Source**
  - Autologous vs Allogeneic
  - Bone Marrow vs Peripheral Blood vs Cord Blood
  - Related vs Unrelated
  - HLA matched vs mismatched
## Sources of Stem Cells for Transplantation

<table>
<thead>
<tr>
<th>Autologous</th>
<th>Allogeneic</th>
</tr>
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<tbody>
<tr>
<td>• Donor available</td>
<td>Undamaged stem cells</td>
</tr>
<tr>
<td>• No GVHD</td>
<td>No tumor contamination</td>
</tr>
<tr>
<td>• No immunosuppression</td>
<td>Graft-vs-tumor effect</td>
</tr>
</tbody>
</table>

*Less toxicity*

*Higher relapse rates*
Allogeneic PBSCT vs BMT

- Engraftment of PBSCs faster than BM
- Acute GVHD ?minimally higher after PBSCT despite much greater T cell number than BM
- Chronic GVHD higher with PBSC
- Immune reconstitution faster with PBSC
Chronic GVHD

- Clinically and pathologically distinct from acute GVHD
- Presentation:
  - lichenoid or sclerodermatous skin involvement
  - cholestasis
  - sicca syndrome
  - GI tract strictures
  - bronchiolitis obliterans
- Poorly responsive to treatment
- Extensive chronic GVHD - high mortality
Histocompatibility Issues

- **Major HLA antigens**
  - located on chromosome 6
  - 1 in 4 likelihood of match with sibling
  - direct sequencing for Class 1 (A, B, C)
  - site specific oligonucleotide probes for Class 2 (DR)

- **Minor HLA antigens**
  - only a handful identified (HA-1, H-Y)
  - routine testing not yet available
  - probably play critical role in GVHD and ? GVL
Unrelated Donor HSCT

- 4 million potential registered donors
- 60-80% of patients can find match
- Likelihood of finding a donor dependent upon racial and ethnic background
- Higher risk of GVHD and graft failure, but lower risk of relapse
- Overall outcome almost equal to MRD
Effect of Single Antigen/Allele HLA Mismatch on Outcome after Unrelated BMT (NMDP)

- HLA -A, -B, -C, and – DR antigen and allele mismatches are all associated with increased GVHD and mortality
- It remains unclear if a mismatch at one particular locus is superior a mismatch at another.
**Umbilical Cord Blood Transplantation**

- Stem cells present in cord blood

- Number of mature T cells low

- UCB transplantation can be performed between 2-3 antigen mismatched donor/patient pairs with low GVHD

- Engraftment and immune reconstitution delayed compared with BM or PBSC
Selection of Cord Blood Unit

- Cell Dose most important factor
  - Cell dose $>3 \times 10^7$ NC/kg optimal
- HLA typing second most important factor
  - 4/6 matched unit or better
- Unknown factors: age of unit, collection method, processing technique
Outcome after Unrelated Cord Blood and Marrow Transplant

Laughlin, et al, NEJM 2004
Double Cord Blood Transplants

- Cell dose is the most important factor to success of cord blood transplant
- Two cords can be infused sequentially which appears to speed engraftment
- Both contribute to early engraftment, but ultimately one cord predominates
Chimerism Patient One

% Chimerism

Days Post Transplant

Recipient
Cord Unit 1
Cord Unit 2

0% 10% 20% 30% 40% 50% 60% 70% 80% 90%

14 28 42 56 72 3 months

Recipient
Cord Unit 1
Cord Unit 2
Complications of HSCT

- Conditioning-related organ toxicity
- Infection
- Graft-versus-host disease
GVHD
Effect on Outcome

- Moderate-to-severe GVHD increases morbidity and mortality of transplantation

- Development of GVHD may prevent disease relapse post-BMT. (CML>>CLL/MDS > AML/ALL).
IBMTR Analysis of Graft-v-Leukemia

Horowitz, Blood 1990;75:555

FOLD DECREASE OR INCREASE IN RISK

RELAPSE

TREATMENT FAILURE

F=0.000

* P=0.04

P=0.02

P=0.04

SEVERITY OF GVHD

NUMBER OF PATIENTS

NONE  MILD  MOD  SEVERE

433  141  72  49

NONE  MILD  MOD  SEVERE

433  141  72  49

NONE  MILD  MOD  SEVERE

433  141  72  49

NONE  MILD  MOD  SEVERE

433  141  72  49
Clinical Evidence for Graft vs. Leukemia Effect

- ✧ Relapse in patients with GVHD
- ↪ Relapse after identical twin transplants
- ↪ Relapse after T-cell depleted transplants
- Durable remissions after donor lymphocyte infusions, not always associated with GVHD
Separating GVL from GVH

- Elimination of leukemia in the absence of lethal GVHD after allogeneic BMT
- LPS antagonism reduces GVHD and preserves GVL activity after experimental BMT
- Il-11 separates GVL effects from GVHD after BMT
- Donor-derived interferon gamma separates GVL effects and GVHD induced by donor CD8+ T cells
Separating GVL from GVH

- G-CSF-mobilized allogeneic SCT maintains GVL effects through a perforin-dependent pathway while preventing GVHD

- Keratinocyte growth factor separates GVL effects from GVHD

- Leucyl-leucine methyl ester-treated haploidentical donor lymphocyte infusions can mediate GVL activity with minimal GVHD risk
Separating GVL from GVH

- Crucial role of timing of donor lymphocyte infusion in generating dissociated GVH and GVL responses in mice receiving allogeneic BMT

- Mixed chimera converted into full donor chimera with powerful GVL effects but no GVHD after non T cell depleted HLA mismatched peripheral blood stem cell transplantation

- Definitive separation of GVL and GVH specific CD4+ T cells by virtue of their receptor beta loci sequences
Strategies to Prevent GVHD

- Interfere with T cell activation/function
  - cyclosporine
  - tacrolimus
  - rapamycin? (sirolimus)
- Interfere with T cell proliferation
  - methotrexate
  - mycophenolate
- Reduce T cell number (T cell depletion)
T Cell Depletion - Advantages

- Decreased incidence and severity of acute GVHD
- Decreased incidence of chronic GVHD
- May eliminate need for immune suppressive medication
- Decrease in organ toxicity
T Cell Depletion - Disadvantages

- Increased rate of graft rejection (early series)
- Increase rate of disease relapse
  - CML clearly
  - less certain with other malignancies
- Increase in EBV lymphoproliferative disease
- Delayed immune reconstitution
## Randomized TCD URD Trial

<table>
<thead>
<tr>
<th></th>
<th>TCD</th>
<th>CyA/Mtx</th>
<th>p</th>
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<tbody>
<tr>
<td>Engraftment</td>
<td>.94</td>
<td>.93</td>
<td>NS</td>
</tr>
<tr>
<td>Gr 3-4 GVHD</td>
<td>.15</td>
<td>.27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>cGVHD</td>
<td>.24</td>
<td>.29</td>
<td>0.10</td>
</tr>
<tr>
<td>Bearman tox.</td>
<td>Less</td>
<td>More</td>
<td>&lt;0.01</td>
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<tr>
<td>Hosp days</td>
<td>32.0</td>
<td>37.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Bact/Fung infx</td>
<td>Same</td>
<td>Same</td>
<td>NS</td>
</tr>
<tr>
<td>CMV infx</td>
<td>More</td>
<td>Less</td>
<td>0.008</td>
</tr>
<tr>
<td>Relapse – CML</td>
<td>0.16</td>
<td>0.06</td>
<td>0.01</td>
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<tr>
<td>Relapse – Ac. Leuk</td>
<td>0.26</td>
<td>0.24</td>
<td>NS</td>
</tr>
<tr>
<td>OS</td>
<td>.31</td>
<td>0.33</td>
<td>NS</td>
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Wagner, et al Lancet 2005
Donor Lymphocyte Infusions

- Can induce patients who have relapsed after BMT into complete remission without use of additional chemotherapy

- Most effective for CML (70-85%) with activity in myeloma, MDS, CLL also noted

- Can cause GVHD
Quantitative PCR Analysis After Allogeneic BMT and DLI for Low Grade Lymphoma
Survival after PBSCT, BMT, or CD34+ PBSCT (+DLI) for CML (Elmaagacli, et al Blood 2003)
Non-Myeloablative Transplantation

- Goal of conditioning is to facilitate engraftment, not eradicate tumor

- Engraftment can be achieved with reduced conditioning

- Early toxicity low and allows transplantation of older patients and those with medical contraindications to high dose therapy –though chronic GVHD a major problem

- Unclear whether superior or inferior to conventional transplantation
Graft Engineering Strategies: Beyond the Average T Cell

- Expansion and infusion of immune suppressive CD4+CD25+ Tregs
- Manipulation of B Cells to treat/prevent chronic GVHD
- Infusion of KIR-mismatched NK Cells to augment GVL and prevent GVH
- Modulation of recipient and host DCs to affect GVHD and GVL
Graft Engineering Strategies

- Insertion of suicide genes (e.g., HSV-TK) which will make T cells susceptible to in vivo destruction during GVHD reaction

- Depletion of activated T cells after co-cultivation of marrow with allo-antigen presenters

- Anergization of T cells (e.g. CTLA4Ig) against alloantigens after co-cultivation with APCs
Gender and GVHD
Male patients with female donors

- Relapse less often
- Suffer more GVHD

Randolph, Blood 2004
Clinical Relevance of H-Y Antibody?

- 75 F→M HSCT patients with plasma collected 6 months to 5 years after HSCT
- Analyze B cell immune responses against five H-Y antigens in relation to:
  1. Donor selection criteria
  2. Transplant and immunosuppressive treatment regimens
  3. Clinical outcome.
Antibody Response to H-Y Antigens correlates with Chronic GVHD

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic GVHD vs. none</td>
<td>15.45</td>
<td>(4.8-50)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

| **Multivariable analysis** |          |           |         |
| Chronic GVHD vs. none      | 55        | (7.6-402) | <0.0001 |

**Variables:**
- Patient age
- Donor age
- Conditioning:
  - Ablative vs Nonmyeloablative
  - Marrow vs PBSC
  - Unrelated vs Related Donor
  - T cell depletion

**Stem Cell Source:**
- Marrow vs PBSC
H-Y antibody: Chronic GVHD and Relapse

Miklos, et al 2004
Outcome after Unrelated Cord Blood and Marrow Transplant (EBMT)

Rocha, et al
NEJM 2004
Donor Lymphocyte Infusions

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- Most effective for CML (70-85%) with activity in myeloma, MDS, CLL also noted
Quantitative PCR Analysis After Allogeneic BMT and DLI for Low Grade Lymphoma
On the Horizon

- Identification of DLI target antigens for future development as tumor vaccines

- Identification of minor histocompatibility antigens and their roles in GVH/GVL

- Development of new drugs which can eliminate transplantation altogether