Disclosure Information

I have no financial relationships to disclose relevant to the content of this presentation.

Current Concepts in Allogeneic Stem Cell Transplantation

Characteristics of Hematopoietic Stem Cells

- **Frequency**: 2-10 stem cells per 10^5 marrow cells
- **Pluripotent**: Give rise to all mature hematopoietic cell types
- **Self-renewing**: Can undergo cell division without differentiation
- **Long-term reconstituting activity**: Between 1 and 10 pluripotent stem cells can repopulate the entire hematopoiesis of a mouse.
- **Quiescent** or only slowly cycling

Sources of Stem Cells

- **Bone marrow**
- **Bloodstream**
- **Cord blood**
First marrow transplantation from an identical twin donor for refractory acute lymphocytic leukemia by Dr. Thomas (Seattle), in 1958. Photo shows patient 4 weeks after transplant (right) and her donor.

History of Blood and Marrow Transplantation

1968 Good: First successful marrow transplant from an HLA-identical sibling
1973 Speck: First marrow transplant from an unrelated donor
1977 Seattle Group: Results of HLA-identical sibling transplants in 100 patients with end-stage leukemia: 13 long-term disease-free survivors
1988 Gluckman: First successful cord blood transplant from an HLA-identical sibling
1990 Thomas: Awarded Nobel Prize in Medicine for endeavors in experimental and clinical bone marrow transplantation

Types of Stem Cell Transplants

**Autologous:** The patient’s own stem cells are used.

**Allogeneic:** Stem cells are obtained from an appropriate related or unrelated donor.

Dr. E. Donall Thomas receives Nobel Prize for Medicine from King Carl Gustav of Sweden.
Stem Cell Transplantation Procedure

1) Harvest of stem cells from patient or appropriate related or unrelated donor:
   a) from pelvic bone in general anesthesia (marrow stem cells)
   b) from arm veins by leukapheresis (peripheral blood stem cells)
   c) from placenta after delivery (cord blood stem cells)

2) Treatment of patient with high dose chemotherapy with or without high dose irradiation of whole body to:
   a) destroy all tumor cells in the body of the patient
   b) suppress the immune system of the patient to prevent rejection of the allogeneic stem cell transplant

3) Infuse stem cells into a central vein of the patient like a blood transfusion.

Collection of Peripheral Blood Stem Cells by Leukapheresis

Intravenous Infusion of Blood Stem Cells
Strategy of Myeloablative Allogeneic Stem Cell Transplant

1) Conditioning with high doses of systemic chemotherapeutic agents with or without additional TBI.

2) High dose therapy is designed to eradicate the underlying disease and suppress the recipient's immune system to prevent graft rejection.

3) Stem cell transplant to "rescue" the patient from the toxic effects of the high-dose conditioning regimen on the bone marrow.

4) Postgrafting immunosuppressive treatment is given to prevent GVHD and to establish long-term graft/host tolerance.

5) Toxicities of high-dose conditioning to GI tract, lung, heart and liver have restricted the use of conventional, myeloablative allogeneic SCT to younger, medically fit patients.

Indications and Numbers of Allogeneic Hematopoietic Stem Cell Transplants Worldwide in 2006

<table>
<thead>
<tr>
<th>Indication</th>
<th>Unrelated Donor (Total N=8,350)</th>
<th>Related Donor (Total N=10,260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>4,000</td>
<td>5,000</td>
</tr>
<tr>
<td>ALL</td>
<td>4,500</td>
<td>5,500</td>
</tr>
<tr>
<td>MDS/MPD</td>
<td>6,000</td>
<td>6,500</td>
</tr>
<tr>
<td>NHL</td>
<td>3,000</td>
<td>3,500</td>
</tr>
<tr>
<td>CML</td>
<td>1,000</td>
<td>1,500</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>2,000</td>
<td>2,500</td>
</tr>
<tr>
<td>Other Leukemias</td>
<td>3,000</td>
<td>3,500</td>
</tr>
<tr>
<td>Other Hematologic Cancer</td>
<td>500</td>
<td>1,000</td>
</tr>
<tr>
<td>Aplastic Anemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other Non-Malignant Disease</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

One-Year Survival after a Myeloablative Conditioning Regimen for Acute Leukemias in any Remission, CML or MDS, Age <50 Years, 1988-2007, by Year of Transplant and Graft Source

Reduced-Intensity Allogeneic Stem Cell Transplantation
Age at Myeloablative SCT versus Age at Diagnosis

<table>
<thead>
<tr>
<th>Median Age (years)</th>
<th>Disease</th>
<th>Allogeneic SCT Recipients (FHCRC)</th>
<th>At Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Related Donor</td>
<td>Unrelated Donor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CML</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>AML</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>NHL</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>MM</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>CLL</td>
<td>51</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>HD</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>MDS</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>40 (n=1428)</td>
<td>35 (n=1277)</td>
</tr>
</tbody>
</table>

Graft-versus-Tumor Effect after Allogeneic Marrow Transplant

Principle of Reduced-Intensity Transplant

Tumor Cell Kill by Donor T-cells Instead of Cytotoxic Chemo-Radiotherapy

Strategy of Reduced-Intensity Stem Cell Transplant

1) Non-myeloablative conditioning with purine analogues and alkylating agents or low-dose TBI to suppress the immune system of the recipient to allow engraftment.

2) Post-transplant immunosuppression with tacrolimus or cyclosporine combined with mycophenolate mofetil and/or anti-T-cell globulin to prevent GVHD and graft rejection.

3) Post-transplant immune manipulation by modifying immunosuppressive treatment or by infusion of donor lymphocytes to increase donor chimerism and/or to improve disease control.
Reduced-Intensity Hematopoietic Cell Transplant

A Comprehensive Cancer Center Designated by the National Cancer Institute

Effect of Post-transplant Immunosuppression on Engraftment of DLA-Identical Marrow Grafts after Different Doses of TBI (Seattle)

<table>
<thead>
<tr>
<th>TBI Dose (cGy)</th>
<th>Post-Transplant Immunosuppression</th>
<th># of Dogs w/Stable Engraftment/ # of Dogs Transplanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>920 cGy</td>
<td>None</td>
<td>20/21</td>
</tr>
<tr>
<td>450 cGy</td>
<td>None</td>
<td>16/39</td>
</tr>
<tr>
<td>450 cGy</td>
<td>Prednisone</td>
<td>7/7</td>
</tr>
<tr>
<td>200 cGy</td>
<td>CSP</td>
<td>0/5</td>
</tr>
<tr>
<td>200 cGy</td>
<td>MTX + CSP</td>
<td>2/5</td>
</tr>
<tr>
<td>200 cGy</td>
<td>MMF + CSP</td>
<td>11/12</td>
</tr>
<tr>
<td>100 cGy</td>
<td>MMF + CSP</td>
<td>0/4</td>
</tr>
<tr>
<td>100 cGy</td>
<td>MMF + CSP + CTLA4Ig*</td>
<td>4/6</td>
</tr>
</tbody>
</table>

* Peptide that binds to B7 and blocks T-cell-activating CD28, B7 pathway

Non-Myeloablative Regimens

<table>
<thead>
<tr>
<th>Center</th>
<th>Regimen</th>
<th>Donor</th>
<th>Postgrafting Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle</td>
<td>Flu + TBI (2 Gy)</td>
<td>MRD, URD</td>
<td>CSP + MMF</td>
</tr>
<tr>
<td>Houston</td>
<td>Flu + Mel</td>
<td>MRD, URD</td>
<td>FK-506 + MTX</td>
</tr>
<tr>
<td>London</td>
<td>Flu + Mel + Campath</td>
<td>MRD, URD</td>
<td>CSP + MTX</td>
</tr>
</tbody>
</table>

Candidates for Reduced-Intensity Stem Cell Transplants

Patients who are ineligible for myeloablative stem cell transplants because of:

1) Age > 55 years (related SCT) or > 50 years (unrelated SCT)
2) Medical contraindications like renal, cardiac or pulmonary insufficiencies.
The Potential Benefits of Allotransplantation Using a Non-Myeloablative Regimen

- Low toxicity and mortality
- Low anticipated late effects
- Treatment of elderly patients is feasible
- Suitable for treatment of patients with comorbid conditions
- Can be carried out on an out-patient basis
- Fast recovery with fewer complications and less infection

Retrospective comparison of (a) transplant-related mortality and (b) relapse in patients over 50 years of age with AML receiving either a myeloablative (MA; n=407) or a reduced-intensity (RIC; n=315) transplant from an HLA-identical sibling (EBMT)

<table>
<thead>
<tr>
<th></th>
<th>MA (n=407)</th>
<th>RIC (n=315)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRM</td>
<td>32%</td>
<td>18%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relapse</td>
<td>41%</td>
<td>24%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Aoudjhane M et al. Leukemia 2005; 19: 2304-2312

Retrospective comparison of (c) leukemia-free survival and (d) overall survival in patients over 50 years of age with AML receiving either a myeloablative (MA) or a reduced-intensity (RIC) transplant from an HLA-identical sibling (EBMT)

<table>
<thead>
<tr>
<th></th>
<th>MA (n=407)</th>
<th>RIC (n=315)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFS</td>
<td>44%</td>
<td>44%</td>
<td>NS</td>
</tr>
<tr>
<td>OS</td>
<td>46%</td>
<td>44%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Aoudjhane M et al. Leukemia 2005; 19: 2304-2312
Probability of Survival After HLA-Identical Sibling Transplants for AML, Age >50 Years, 1998–2006
By Disease Status and Conditioning Regimen Intensity

Early, myeloablative (N=660)
Early, reduced-intensity conditioning (N=544)
Intermediate, myeloablative (N=106)
Intermediate, reduced-intensity conditioning (N=777)

P = .3745.

Probability of Survival After HLA-Identical Sibling Allotransplants for Follicular Lymphoma, 1998–2006
By Disease Status and Conditioning Regimen

Chemosensitive, myeloablative (N=316)
Chemosensitive, reduced-intensity conditioning (N=325)
Chemoresistant, myeloablative (N=69)
Chemoresistant, reduced-intensity conditioning (N=46)

P = .0127.

By Donor Type and Conditioning Regimen

HLA-identical sibling, reduced-intensity conditioning (N=175)
HLA-identical sibling, myeloablative (N=238)
Autotransplant (N=1,769)

P = .0001.

Study
Diagnosis
Procedure
OS, %
DFS, %

Maloney
Relapsed, refractory or untreated myeloma
Auto / Matched Sib
94
78
55

Bruno
Newly diagnosed myeloma
Double auto
Auto / Matched Sib
46
45
20
50

Antin JA. Hematology 2007; 47-54
Conclusions

1. Reduced-intensity transplants are most successful in less aggressive diseases such as low-grade lymphomas and chronic lymphocytic leukemia because a graft-versus-tumor reaction takes several weeks to develop after transplant.

2. More aggressive diseases like AML, MDS or aggressive lymphomas have best results with RIC transplants if diseases are in complete remission at the time of transplant.

3. One strategy to obtain both dose intensity and a graft-versus-malignancy effect is to follow a high-dose autologous transplant with a RIC allogeneic transplant. This has been shown, for instance, in multiple myeloma to improve both event-free and overall survival.

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