(Hematopoietic) Stem Cell Transplant Updates

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Objectives

• Understand donor sources for HSCT
• Understand reduced intensity HSCT
• Know indications for HSCT
Stem Cell Transplant Principles

- Dose Intensity (ablative, reduced intensity, nonmyeloablative)

- Stem Cell Rescue

- Immune System Recovery
Dose-Response Curve

- High Growth Tumor Fraction
- Low Growth Tumor Fraction

Response

Increasing Dose

0 2x 4x 6x 8x 10x
Death due to Organ Toxicity

Death due to Marrow Toxicity

Dose

Therapy Required for Cure
Hematopoietic Stem Cell Properties

- Capable of producing all blood cell lines
- Capable of self renewal
- Rare in resting peripheral blood
- Has marker called CD 34
Steps in Stem Cell Transplant

- Prior therapy to decrease tumor burden
- Disease and Functional Testing
- Choose Donor (auto vs. allo)
- Transplant Regimen
  - Cytoreductive
  - Immunosuppressive
- Period of Neutropenia
- Count Recovery
Hematopoiesis
Stem Cell Collection: Harvesting Stem Cells From Bone Marrow or Blood

Donor bone marrow cells repopulate recipient bone marrow
Stem Cell Collection: Peripheral Blood

* Filgrastim
  Plerixafor
  +/- Chemotherapy

Peripheral blood count and CD34+ monitor

Apheresis to collect
>2x10^6 CD34+ cells/kg Auto
>4x10^6 CD34+ cells/kg Allo

* For MUD use filgrastim only
Allogeneic Stem Cell Sources by Recipient Age 2001-2010

Available at: http://www.cibmtr.org
Trends in Transplants by Type and Recipient Age*2001-2010

* Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma
HSCT: Autologous

**Advantages**
- Available for most patients
- No graft vs. host disease
- Regimen can be optimized for antitumor activity
- Low morbidity & mortality
- Few long-term complications

**Disadvantages**
- Contamination with tumor
- Stem cell damage from prior cytotoxic therapy
- No graft vs. tumor reaction
Allogeneic Stem Cell Transplant

• True Transplant of the Immune System
• Need to Find a Donor
  • Sibling
  • Unrelated
  • Cord Blood
  • Haplo-identical
• Cytopenic Phase
• Immunosuppressive therapy early and late
Allogeneic Stem Cell Transplant

• Disadvantages
  • Lack of compatible donors (sibling, unrelated, cord, haploidentical)
  • Graft vs. Host Disease
  • Prolonged immunosuppression necessary
  • Higher morbidity & mortality

• Advantages
  • No contamination with tumor
  • Graft vs. tumor reaction
  • No exposure to prior therapy (in stem cells)
KEY POINTS

• The majority of patients who need a potentially curative allogeneic transplant but lack a suitable matched related donor will be able to find an alternative donor.

• Advances in the supportive care have improved the safety and efficacy of alternative donor transplantation.

• Available retrospective data suggest similar long-term outcomes after transplantation with different types of alternative donors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unrelated adult volunteer donor</th>
<th>Mismatched-related donor</th>
<th>Umbilical cord blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability</td>
<td>20–80%, depending upon recipient ethnicity</td>
<td>Nearly 100%</td>
<td>Nearly 100%</td>
</tr>
<tr>
<td>Cell dose</td>
<td>Collection targeted to recipient weight</td>
<td>Collection targeted to recipient weight</td>
<td>Fixed to what is in UCB bag</td>
</tr>
<tr>
<td>HLA match</td>
<td>7–8/8 considering HLA A, B, C and HLA-DRB1 at the allele level</td>
<td>4–6/8 considering HLA A, B, C and HLA-DRB1 at the allele level</td>
<td>4–6/6 considering HLA A and B antigen and HLA-DRB1 allele level</td>
</tr>
<tr>
<td>Time to find suitable donor</td>
<td>8–10 Weeks</td>
<td>&lt;4 Weeks</td>
<td>&lt;4 Weeks</td>
</tr>
<tr>
<td>Time to neutrophil engraftment</td>
<td>15–20 Days</td>
<td>15–20 Days</td>
<td>20–28 Days</td>
</tr>
<tr>
<td>Risk of graft failure</td>
<td>5%</td>
<td>5–10%</td>
<td>5–15%</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>50–80%</td>
<td>25–50%</td>
<td>25–60%</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>50–60%</td>
<td>10–50%</td>
<td>30%</td>
</tr>
<tr>
<td>Additional cell therapy</td>
<td>Donor lymphocytes are available if needed for delayed engraftment or relapse</td>
<td>Donor lymphocytes are available to treat relapse; experience is limited</td>
<td>Not available</td>
</tr>
</tbody>
</table>

GVHD, graft-versus-host disease.
Unrelated Donor Stem Cell Sources by Recipient Age 2001-2010

Transplants, %

- Bone Marrow (BM)
- Peripheral Blood (PB)
- Cord Blood (CB)

HSCT: Complications

- Toxicity of Preparative Regimen
  - Mucosal, Liver, Lung, Heart
- Myelosuppression, Immunosuppression
  - Infection, Hemorrhage
- Graft vs. Host Disease (allo only)
  - Acute  80% (20-40% severe)
  - Chronic  30%
- Overall Mortality
  - Allogeneic:  10-40%
  - Autologous:  1-5%
Causes of Death after Transplants Done in 2009-2010

Unrelated Donor
- Primary Disease (37%)
- New Malignancy (1%)
- GVHD (18%)
- Infection (18%)
- Other (18%)
- Organ Failure (8%)

HLA-identical Sibling
- Primary Disease (49%)
- GVHD (16%)
- Infection (13%)
- Other (16%)
- Organ Failure (5%)
- New Malignancy (1%)
One-year Survival by Year of Transplant, Donor and Age, Worldwide, 1997-2010

- In any remission, Acute Leukemia, CML or MDS -

What is GVHD?

• Only true genetically identical match = identical twin transplant

• Minor immunologic discrepancies exist between HLA matched donor/recipient pairs

• Donated stem cells grow → mature WBC
  • potential to recognize donor/recipient immunologic disparities and mount immunologic attack against host, resulting in GVHD
Why?

• Conditioning regimen
• Host tissue damage and cell activation
• Inflammatory cytokines released from host cells
• TNF-α, IL-1, IL-6
Graft vs Host Disease

<table>
<thead>
<tr>
<th>Acute GVHD</th>
<th>Chronic GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 days post transplant</td>
<td>&gt;100 days post transplant</td>
</tr>
<tr>
<td>Skin, liver, GI tract</td>
<td>Skin, liver, eyes, mouth, GI</td>
</tr>
<tr>
<td></td>
<td>tract</td>
</tr>
</tbody>
</table>
Maculopapular rash
Oral manifestations
Hypo and Hyper pigmentation of the skin
Autologous vs. Allogeneic Transplant

- Donors Easily Available
- Regimen Tailored
- Potential Tumor Contamination
- Low Morbidity / Mortality
- No GVHD/GVT
- Few Long Term Complications
- Major Risk Relapse

- Must Find Donor
- Regimen must be Immunosuppressive
- Higher Morbidity/ Mortality
- GVHD both Acute and Chronic as Major Complication
- GVT Effect
- Lower Risk of Relapse
Which Patients Should be Considered for Transplant?

- **Non-malignant disease**: aplastic anemia, thalassemia, life threatening immunodeficiency state→frequently cured by **Allo HSCT, Auto HSCT** for autoimmune disorders

- **Malignant disease**: Hematological malignancies and certain other solid tumors
  - **Allo HSCT** is the only chance of cure for relapsed AML, ALL, relapsed NHL, or Hodgkin’s disease
  - **Allo HSCT** is the only chance of cure for CLL and Myelodysplasia, Myeloproliferative disorder
  - **Auto HSCT** can be used to cure relapsed NHL and Hodgkin’s disease
  - **Auto HSCT** can extend DFS and OS in multiple myeloma BUT IS NOT CURATIVE.
  - **Auto HSCT** used to restore hematopoiesis after the administration of high dose chemotherapy in certain solid tumors, breast cancer, neuroblastoma, and germ cell tumors
Indications for Hematopoietic Stem Cell Transplants in the United States, 2010
(Inflation factor: Auto=1.25 (80%), Allo=1.05 (95%), All Transplants)

Number of Transplants

- Multiple Myeloma
- NHL
- AML
- ALL
- MDS/MPD
- HD
- CML
- Aplastic Anemia
- Other Leuk
- Non-Malignant Disease
- Other Cancer

Allogeneic (Total N=8,860)
Autogeneic (Total N=9,026)
Disease States and Transplant Types (as a general rule)

- Autologous
  - Multiple myeloma
  - Relapsed Hodgkin's disease
  - DLBCL: relapsed and refractory
  - Non-Hodgkin Lymphoma
  - Germ cell Tumors
  - Ewing's Sarcoma
  - T cell lymphoma is first remission

- Allogeneic
  - AML
  - ALL
  - CML
  - CLL
  - Hemoglobinopathies
  - Relapsed NHL after Allo
  - T cell lymphoma at relapse
Nonmyeloablative Transplant/Reduced Intensity Transplants

• Less intense chemotherapy
• Older patients now feasible
• Decreased mucositis
• Shift to outpatient therapy
• Less transfusion requirements
• No change in Chronic GVHD/GVL
• Increase Patient Eligibility
  • No true upper age limit
  • Allows for impairment of:
    • Cardiac
    • Pulmonary function
    • Hepatic
    • Renal

• Infection not absolute contraindication
<table>
<thead>
<tr>
<th>Functional Status</th>
<th>MYELOABLATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 60 (TBI (\geq) 1200 cGy); &lt; 65 (Flu/Bu, Bu/Cy)</td>
</tr>
<tr>
<td>ECOG score</td>
<td>0 or 1</td>
</tr>
<tr>
<td>KPS</td>
<td>(\geq) 70%</td>
</tr>
<tr>
<td>HCT-CI</td>
<td>(\leq) 3</td>
</tr>
</tbody>
</table>

**Organ Function**

- **Cardiac**: Ejection fraction \(\geq\) 40%
- **Hepatic**: Bilirubin \(\leq\) 2X ULN\(^1,2\), AST/ALT \(\leq\) 3X ULN
- **Pulmonary**: DLCO\(_{corrected}\) \(\geq\) 40%, and FEV\(_1\) \(\geq\) 50\(^1\)
- **Renal**: Creatinine clearance \(\geq\) 50 ml/min

**Donor Selection**

- HLA match: HLA 8/8, 7/8\(^3\), or 6/8\(^4\) match

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1 Unless clearly disease-related.
2 If total bilirubin > 2X ULN, but direct bilirubin normal, patient will be considered eligible.
3 7/8 matches must also be matched at least one DQB1 antigen [minimum 8/10 match]
4 6/8 matches must also be matched at both DQB1 antigens [minimum 8/10 match]
<table>
<thead>
<tr>
<th>Functional Status</th>
<th>NonMyeloablative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;= 75</td>
</tr>
<tr>
<td>ECOG score</td>
<td>&lt;= 2</td>
</tr>
<tr>
<td>KPS</td>
<td>&gt;= 60%</td>
</tr>
<tr>
<td>HCT-CI</td>
<td>No restriction</td>
</tr>
</tbody>
</table>

### Organ Function

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Ejection fraction &gt;= 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic</td>
<td>Bilirubin &lt;= 2X ULN(^1,2), AST/ALT &lt;= 3X ULN(^1)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>DLCO(_{corrected}) &gt;= 40%, and FEV1 &gt;= 40%(^1)</td>
</tr>
<tr>
<td>Renal</td>
<td>Creatinine clearance &gt;= 40 ml/min</td>
</tr>
</tbody>
</table>

### Donor Selection

| HLA match         | Age 70 – 75: 10/10 match. Age 65 – 69: 8/8 or 7/8 match\(^3\). Age < 65: see Table 1 |

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\(^1\)Unless clearly disease-related.  
\(^2\)If total bilirubin > 2X ULN, but direct bilirubin normal, patient will be considered eligible.  
\(^3\)37/8 matches must also be matched at both DQB1 antigens [min...
Take Home Messages

• No true upper age limit for HCT
• Alternative donor sources becoming more feasible (Haplo HCT)
• Never too early to refer
Thank You!!!!

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