Where in the TED
Does HCT Stuff Go?

Diane J. Knutson

Key Concepts

- What is an HSCT?
- Why perform one?
- Who can benefit?
- Mechanics of transplant
- Early and Late complications
- Where on "new" TED?

Introducing Pre-TED & Post-TED
Blood is Made in the Bone Marrow

- Axial skeleton
- Inner spongy bone
- Bone marrow is in the holes
- Bone marrow is a highly organized/regulated organ

Bone Marrow: The Source of Blood and Our Immune System

- Blood stem cells
  - Pluripotent
  - Self renewing
- Highly regulated production
  - Cytokines (SCF, IL3)
  - Growth factors (G-CSF)

Hematopoiesis Scheme
**Goals of HSCT**

- Provide stem cell replacement
  - Autologous and allogeneic
- Destroy malignancy
  - Potentially lethal chemotherapy/radiation
  - Immunotherapy

![Indications for Allogeneic Hematopoietic Stem Cell Transplants, 2003 – Worldwide](image)

![Pre-TED AML](image)
100-day Mortality after HLA-identical Sibling Myeloablative Transplants, 2002-2003

Mortality, %

- 1st Complete Remission
- 2nd Complete Remission
- Not in Remission
- Chronic Phase
- Accelerated Phase
- Blast Phase

AML ALL CML MDS Aplastic Anemia Immune Deficiency

Acute Leukemia section

Hematopoietic Stem Cell Transplantation

- Allogeneic
  - HLA-identical sibling
  - Other related
- Autologous
- Donor

Bone marrow
Peripheral blood
Umbilical cord blood

Collection
Manipulation

Negative Positive
Ex vivo
selection
expansion

Negative Positive
Ex vivo
selection
expansion
Basics of HLA

- HLA = human leukocyte antigens
- Proteins on cell surfaces that are key players in immune response

HLA

- Class 1 = HLA-A, B, C
- Class 2 = HLA-DR, DP, DQ
- Differ in types of organisms they recognize and cells on which they are found

HLA Compatible Donor

- Varies among HSCT centers
- Varies among protocols
- Current acceptable donor
  - A, B – serologic match?
  - DRB1 – allele match
**Antigen vs Allele**

- **Antigen** = protein on surface of cells (serology)
- **Allele** = gene (DNA)

**What is a “Match”?**

<table>
<thead>
<tr>
<th>P:</th>
<th>A1, A2, DR1</th>
<th>A<em>0101, A</em>0201, DRB1*0101</th>
</tr>
</thead>
<tbody>
<tr>
<td>B7, B8, DR3</td>
<td>B<em>0702, B</em>0801, DRB1*0301</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D:</th>
<th>A1, A2, DR1</th>
<th>A<em>0101, A</em>0301, DRB1*0101</th>
</tr>
</thead>
<tbody>
<tr>
<td>B7, B8, DR3</td>
<td>B<em>0702, B</em>0803, DRB1*0304</td>
<td></td>
</tr>
</tbody>
</table>

**DNA-Based**

**Serology**

**Pre-TED Donor Type**

- **Donor Type:**
  - HLA-A
  - HLA-B
  - HLA-C
  - Other

- **Degree of sharing:**
  - Identical
  - HLA-matched
  - HLA-unmatched

- **Allelic match:**
  - Allelic
  - Other

- **Matched and unmatched donor (MUC):**
  - Matched
  - Other

- **HLA-matched unrelated donor (MUC):**
  - Matched
  - Other
Hematopoietic Stem Cell Transplantation

Allogeneic
- HLA-identical sibling
- Other relative
- Bone marrow
- Peripheral blood
- Umbilical cord blood
- Unrelated

Autologous
- Bone marrow
- Peripheral blood
- Umbilical cord blood

Donor

Collection

Manipulation

Timeline of HSCT

Complications:
- Antibiotics
- Nutrition
- Antiemetics
- Growth factors
- Red cell transfusions
- Platelet transfusions
- Donor search or obtain autologous stem cells
- Chemo XRT
- PBSC/BM harvests in ABMT
- Secondary tumors, cataracts, endocrine changes, QoL
- Acute and/or chronic GvHD
- Viral infections
- CMV, VZV, PCP, IP
- Bacterial infections
- HSV mucositis
- VOD
- BM/SC re-infusion
- Marrow function
- Immune function

Supportive Therapy:
- DHAP and GF and PBSC
- Collect & freeze

Slide 2

Allogeneic Stem Cell Sources by Recipient Age 1997-2004

Transplants, %

<table>
<thead>
<tr>
<th>1997-2000</th>
<th>2001-2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow (BM)</td>
<td>Peripheral Blood (PB)</td>
</tr>
<tr>
<td>Ages ≤20 yrs</td>
<td>Ages &gt;20 yrs</td>
</tr>
</tbody>
</table>
### Pre-TED Graft Manipulation

> Was there *in vivo* graft manipulation either for RBC removal or volume reduction? Yes/No
> 
> (Check all that apply): Options for non-U.S. Centers
> 
> - Total depletion
> - Tumor purging
> - Cord selection
> - Other, specify: ________________

### Most Commonly Used Preparative Regimen Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>HLA-ident sib BMT-malignancy</th>
<th>Unrelated Donor BMT-malignancy</th>
<th>Auto-HSCT Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI</td>
<td>52%</td>
<td>85%</td>
<td>25%</td>
</tr>
<tr>
<td>Cytoxan</td>
<td>87%</td>
<td>91%</td>
<td>85%</td>
</tr>
<tr>
<td>Busulfan</td>
<td>48%</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Etoposide</td>
<td>24%</td>
<td>19%</td>
<td>73%</td>
</tr>
<tr>
<td>Ara-C</td>
<td>5%</td>
<td>10%</td>
<td>25%</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>4%</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Platinum*</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>7%</td>
</tr>
<tr>
<td>Nitrosourea**</td>
<td>1%</td>
<td>&lt;1%</td>
<td>53%</td>
</tr>
</tbody>
</table>

* cis-Platinum / carboplatin  ** BCNU / CCNU

### A Continuum of Non-myeloablative/Reduced Intensity Prep Regimens

- **Immunosuppression**
  - Haplo / T-cell Dep
  - MUD
  - Matched sibling

- **Myelosuppression**
  - CLL / LGL
  - CML
  - LCL
  - MM
  - AML

<table>
<thead>
<tr>
<th>Aggressiveness Of Malignancy</th>
<th>CLL / LGL</th>
<th>CML</th>
<th>LCL</th>
<th>MM</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI 2Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+Cy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+ATG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+TT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+Cy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+TT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+ATG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+TT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+ATG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+TT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+ATG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+TT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+ATG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+TT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+ATG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI+F+TT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Allogeneic Transplants, Registered with the CIBMTR, 1998-2004

Pre-TED Preparative Regimen

Trends in Autologous Transplants Recipient Age* 1993-2004

* Data incomplete

* Transplants for AML, ALL, NHL, Hodgkin disease, Multiple Myeloma
Enhance/Monitor Recovery

- Administer growth factors
  - G-CSF, GM-CSF
- Monitor hematopoietic recovery
  - Cell number and type (granulocytes, platelets, etc.)
  - Marrow cellularity
  - Chimerism (X/Y, VNTR, HLA)

ANC recovery (not engraftment)

- Report first of three consecutive days of ANC greater than 500
- Usually not before 8-10 days for myeloablative HSCT
- May never become neutropenic for reduced-intensity

Post-TED ANC Recovery

**After HSCT**
- Initial ANC recovery (Neutrophils ≥ 0.5 x 10^9/L)
  - Yes, date Neutrophils ≥ 0.5 x 10^9/L
  - No, date of last assessment
- Never below
- Previously reported
- Unknown
Did graft failure occur?  Yes  No
Complications

- Graft rejection
- Graft vs host disease
- Relapse of disease
- Infection
- Regimen-related toxicity

Graft vs Host Disease/Graft Rejection

HLA differences stimulate detrimental immune responses

Factors Influencing Risk Of GVHD

Donor/Graft-related
- HLA-disparity
- Female → Male
- Parity
- Older age
- T-cell dose
- AGVHD (for CGVHD)

Recipient-related
- Older age
- Prior viral infection/exposure
- Other microbial infection

Treatment-related
- Conditioning regimen
- Inadequate immune suppression
### Acute GVHD Glucksberg Staging (organs) Criteria

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver (Bilirubin)</th>
<th>Intestinal tract *&lt;br&gt;(diarrhea)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>No rash</td>
<td>&lt;2.0 mg/dL or &lt;35 mmol/L</td>
<td>None or &lt;500 ml/day or &lt;280 ml/m²/day</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Maculopapular rash, &lt;25% of body surface</td>
<td>2.0-3.0 mg/dL or 35-52 mmol/L</td>
<td>600 but &lt;1000 ml/day or 280-555 ml/m²/day</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Maculopapular rash, 25-50% of body surface</td>
<td>3.1-6.0 mg/dL or 53-103 mmol/L</td>
<td>&gt;1000 but &lt;1500 ml/day or 556-833 ml/m²/day</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Generalized erythroderma</td>
<td>6.1-15.0 mg/dL or 104-236 mmol/L</td>
<td>&gt;1500 ml/day or &gt;833 ml/m²/day</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Generalized erythroderma with bullae formation and desquamation</td>
<td>&gt;15.0 mg/dL or &gt;356 mmol/L</td>
<td>Severe abdominal pain, with or without ileus</td>
</tr>
</tbody>
</table>

*use ml/day for adult patients and ml/m²/day for pediatric patients

---

### Overall Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Stage 1 to 2 skin rash; no gut involvement; no liver involvement; no decrease in clinical performance</td>
</tr>
<tr>
<td>Grade II</td>
<td>Stage 1 to 3 skin rash; Stage 1 gut involvement or liver involvement (or both); mild decrease in clinical performance</td>
</tr>
<tr>
<td>Grade III</td>
<td>Stage 2 to 3 rash; Stage 2 to 3 gut involvement or Stage 2 to 4 liver involvement (or both); marked decrease in clinical performance</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Similar to Grade II with Stage 2 to 4 organ involvement and extreme decrease in clinical performance</td>
</tr>
</tbody>
</table>


---

### Chronic GVHD

- Poorly understood late manifestation
  - Both alloimmune and autoimmune features
  - In part a failure of thymus function
- Incidence
  - ~1/3 of matched sibs
  - 60-70% of matched unrelated
  - Higher with mismatched
- Risk factors
  - HLA disparity, patient age, prior aGVHD, graft source
Chronic GVHD Classification
(old but it’s what we’ve got)

- Limited
  - Either or both
    - Localized skin involvement
    - Hepatic dysfunction due to cGvHD

Chronic GVHD Classification continued

- Extensive
  - Generalized skin involvement, or
  - Localized skin involvement and/or hepatic dysfunction due to chronic GvHD
  - OR
    - Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis, or
    - Eye involvement (Schirmer test <5mm wet), or
    - Involvement of minor salivary glands/oral mucosa
    - Involvement of any other organ

Manifestations Of Chronic GVHD (I)

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Definite manifestations of Chronic GVHD</th>
<th>Possible manifestations of Chronic GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Scleroderma (superficial or fasciitis), lichen planus, vitiligo, scarring alopecia, hyperkeratotic papules, contractures from skin immobility, nail bed dysplasia</td>
<td>Eczematoid rash, dry skin, maculopapular rash, hyperpigmentation, hair loss</td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>Lichen planus, non-infectious ulcers, corneal erosions/non-infectious conjunctivitis</td>
<td>Xerostomia, keratoconjunctivitis sicca</td>
</tr>
<tr>
<td>GI tract</td>
<td>Esophageal strictures, steatorrhea</td>
<td>Anorexia, malabsorption, weight loss, diarrhea, abdominal pain</td>
</tr>
<tr>
<td>Liver</td>
<td>None</td>
<td>Elevation of alkaline phosphatase, transaminases, cholangitis, hyperbilirubinemia</td>
</tr>
</tbody>
</table>
Manifestations Of Chronic GVHD (II)

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Definite manifestations of Chronic GVHD</th>
<th>Possible manifestations of Chronic GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>None</td>
<td>Elevation of alkaline phosphatase, transaminitis, cholangitis, hyperbilirubinemia</td>
</tr>
<tr>
<td>GU</td>
<td>Vaginal stricture, lichen planus</td>
<td>Non-infectious vaginitis, vaginal atrophy</td>
</tr>
<tr>
<td>Musculoskeletal/serosa</td>
<td>Non-septic arthritis, myositis, myasthenia, polyserositis, contractures from joint immobilization</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Hematologic</td>
<td>None</td>
<td>Thrombocytopenia, eosinophilia, autoimmune cytopenias</td>
</tr>
<tr>
<td>Lung</td>
<td>Bronchiolitis obliterans</td>
<td>Bronchiolitis obliterans with organizing pneumonia, interstitial pneumonitis</td>
</tr>
</tbody>
</table>

Post-TED GVHD

GVHD (Also only)

Maximum Grade of Acute Graft Versus Host Disease (GVHD): I, II, III, IV, Unknown

Maximum extent of Chronic GVHD: None, Limited, Extensive, Unknown

Data of diagnosis of chronic GVHD: [MM/DD/YYYY]

Continued from last report

Evaluating Post-HSCT Disease Status

- Most frequent cause of treatment failure
- Vigilance may affect rapidity of diagnosis
- Method of detection really does matter
Method of Detection of Disease

- Molecular (most sensitive)
  - Blood or marrow
  - Bcr/abl, bcl-2
- Cytogenetic (mod. sensitive)
  - Blood or marrow
  - t(9:22), t(14:18)
- Hematologic (least sensitive)
  - Blood or marrow appearance

Post-TED Disease Assessment

- Relapse prophylaxis ("planned")
- Treatment of relapse: CML, AML
- Treatment of PTLD, EBV-Lym
- Treatment of GVHD
- Treatment of Viral Infections
- Chimerism
  - Stable or declining donor cells
- Other emerging indications
Post-TED DCI

Causes of Death after Transplants Done in 1998-2002

Post-TED Survival

Survival status at latest follow-up:

- Alive
- Dead
- LTF

Latest follow-up:
- Last known date alive:
- Date estimated

Main cause of death (check only one main cause):

- Relapse/Progression/Persistent disease
- GvHD-related causes (check as many as appropriate)
- Infection
- Other

Post-TED Survival
Late Complications of BMT

- Regimen-related toxicity
  - Cataracts
  - Neurologic
  - Gonadal
  - Endocrine
  - Growth & development
- Infection
- Chronic GVHD
- Relapse of malignancy/New-2nd cancers

Post-TED Second Cancer

Factors Affecting HSCT Success

- Diagnosis and stage of disease
- Time from diagnosis to HSCT
- Quality of HLA match
- Ages of recipient/donor
- Prior CMV exposure
- Disease treatment
- HSCT protocol
Information on persons treated under ordinary circumstances, with treatments selected by the recipients, by clinical judgements of physicians, or by nature rather than by experimental design.