BMTCN Review Course

Basic Concepts and Indications for Transplantation

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• No disclosures
Objectives

• Describe basic concepts of transplantation
• Describe indications for transplantation for malignant and non-malignant diseases

Note the primary reference sources for this course are:


Hematopoietic Stem Cell Transplantation

**Autologous Transplant**
Stem cells are harvested from the patient, frozen and then reinfused after high-dose chemotherapy.
Hematopoietic Stem Cell Transplantation

**Allogeneic Transplant**

After a patient undergoes high-dose treatment, stem cells are collected from a donor and infused into the patient soon thereafter.
Immunology of transplantation

• Pluripotent
  – Able to self-replicate, proliferate and differentiate
    • Red blood cells
    • Platelets
    • White blood cells
      – Myeloid
        » Neutrophils, basophils, granulocytes, macrophages
      – Lymphoid
        » T and B lymphocytes

• Ability to “hone” to bone marrow spaces after IV infusion
  – Mechanism not fully understood
  – The microenvironment of the bone marrow

• Can be safely cryopreserved – allowing for storage and future use
Brief history of transplantation

1945 - WWII

• Hiroshima - severe effects of radiation on the production of hematopoietic cells
• 1949 – Mice with spleen shielded survived lethal radiation, supporting the role of humoral immunity
• 1958 – human marrow infused into victim of radiation exposure
• 1959 AUTO HCT for CML (successful engraftment; unsuccessful treatment)
• 1959 – Syngeneic (identical twin) experiment in leukemic patient – survived 3 months
Brief history of transplantation

Case reports of transplantation between 1958 and 1968

- 203 reports
  - Graft failure – 125
  - GVHD – 47
  - Survival – 0
- Mid – late 1960s, studies of histocompatibility typing
- 1968 - first allogeneic HCT for children with immune deficiencies
- 1975 – studies of Total Body Irradiation in dogs
  - Single dose fatal
  - Fractionated doses tolerated and dogs engrafted
  - Continued problems with graft failure and GVHD
1968 Canine Long-Term Survivors
Human Leukocyte Antigen (HLA)

Major Histocompatibility Complex (MHC) are cell surface markers which mediate interactions of leukocytes (WBCs). The markers reside on chromosome 6. They are genetically inherited. For HCT, there are six major antigens.
Brief history of transplantation

Mid to late 1970s and 1980s

- Addition of Cyclophosphamide
- Methotrexate as post transplant immunosuppression
- Discovery of Cyclosporin
- Addition of Antithymocyte Globulin (ATG)
- Successful human transplants with HLA-identical bone marrow
- National Marrow Donor Program began in 1986
Brief history of transplantation

1990s

• Collection of Peripheral Blood Progenitor Cells began
  • Cryopreservation technology developed
• Tacrolimus in combination with MTX
• 1991 Filgrastim (Neupogen, GCSF) is FDA approved
• 1995 Parma AUTO HCT superior to salvage for aggressive NHL
• 1996 Schmidtz AUTO PBSC versus BM
• 1996 AUTO HCT for Multiple myeloma
• E.D. Thomas / Seattle – Nobel Prize
• Graft versus tumor (GVT or GVL) effect
• Reduced intensity transplantation
City of Hope Transplant Highlights

• 1976 – COH program begins under the direction of Karl Blume and Ernest Beutler
  • Stephen Forman joined in 1978
• 1976 – 3 bed unit on Machris – performed 6 transplants
• Significant contributions to field
  • Reduced intensity transplants
  • Total Marrow Irradiation
  • Modified T cell therapies
  • GVHD prevention
  • CMV treatment and prevention
  • Transplant for HIV associated lymphomas
COH rates for one-year survival are among the best. In the US, only City of Hope has performed above expectation for ten consecutive reporting years. City of Hope also received a score of exceptional performance for unrelated donor transplant survival (one of only three centers to receive this score).

Predicted one-year survival: 67.7% / Actual one-year survival: 75.2%
### Ages at Diagnoses vs. Ages at Myeloablative HCT

<table>
<thead>
<tr>
<th>Disease</th>
<th>Median Ages (years)</th>
<th>At Diagnoses (SEERS)</th>
<th>Recent Allogeneic HCT Recipients (FHCRC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Related Donor</td>
</tr>
<tr>
<td>CML</td>
<td>67</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>AML</td>
<td>68</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>NHL</td>
<td>65</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>MM</td>
<td>70</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>CLL</td>
<td>71</td>
<td>51</td>
<td>46</td>
</tr>
<tr>
<td>HD</td>
<td>34</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>MDS</td>
<td>68</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>68</strong></td>
<td><strong>40 (n=1428)</strong></td>
<td><strong>35 (n=1277)</strong></td>
</tr>
</tbody>
</table>
Parma study for relapsed aggressive NHL

Relapsed aggressive NHL
BM(-)
n=215

DHAP x 2
CR/PR
(n=125)

RANDOMIZE
n=109

DHAP x 4

HDT/ABMT

ABMT is superior to salvage chemotherapy for relapsed chemosensitive aggressive NHL.

Advances in Support Care and Evidence Based Medicine Practices

- Acyclovir for HSV and VZV reactivation prevention
- Gancyclovir prophylaxis for CMV
- Fluconazole prophylaxis for fungus
- Bactrim prophylaxis for PJP
- Broad spectrum antibiotics
- Better blood component screening and transfusion medicine practices
- Anti-emetic and nutritional support
- Analgesia pain management practices
- Post transplant therapies (e.g. DLI, Rituximab, Bortezomib, anti-CD30, others)
- Standardized guidelines to manage the complications of patients undergoing HDT/ASCT
Hematopoietic Stem Cell Transplantation

Autologous Transplant
Stem cells are harvested from the patient, frozen and then reinfused after high-dose chemotherapy.
Hematopoietic Stem Cell Transplantation

Allogeneic Transplant
After a patient undergoes high-dose treatment, stem cells are collected from a donor and infused into the patient soon thereafter.
## Comparison of PBPC (peripheral blood progenitor cell) and BMT (autologous bone marrow transplant)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PBPC</th>
<th>BMT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization (days)</td>
<td>17</td>
<td>23</td>
<td>.002</td>
</tr>
<tr>
<td>Neutrophil recovery (days)</td>
<td>11</td>
<td>14</td>
<td>.005</td>
</tr>
<tr>
<td>Platelet recovery (days)</td>
<td>16</td>
<td>23</td>
<td>.02</td>
</tr>
<tr>
<td>Platelet transfusions (days)</td>
<td>6</td>
<td>10</td>
<td>.001</td>
</tr>
<tr>
<td>RBC transfusions (number)</td>
<td>2</td>
<td>3</td>
<td>.002</td>
</tr>
</tbody>
</table>

Transplant Process (5 steps)

(1) Conditioning
(2) Stem cell infusion
(3) Neutropenic phase
(4) Engraftment phase
(5) Post-engraftment period
Typical Time Course for High-dose Therapy and Autologous Stem Cell Transplantation

- Radiation
- Chemotherapy
- Stem cell infusion
- Neutropenia
- Engraftment

Day: -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 +1 +2 +3 +4 +5 +6 +7 +8 +9 +10 +11 +12 +13 +14

WBC
Indications for HCT

• Autologous
  • Diseases not involving the bone marrow – or where previous treatment has eradicated the disease from the bone marrow
    – Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Multiple myeloma, Systemic Amyloidosis
    – Certain solid tumors (germ cell, Neuroblastoma)
    – Investigational: Autoimmune disorders
Indications for HCT

• Allogeneic
  • Diseases of the blood and bone marrow
    – Acute and chronic leukemias, Myelodysplastic syndrome, certain lymphomas
  • Non-malignant Hematologic disorders
    – Aplastic anemia
  • Primary immunodeficiencies and hemoglobinopathies
Indications for Hematopoietic Stem Cell Transplants in the US, 2012

- **Allogeneic (Total N=7,554)**
- **Autologous (Total N=11,145)**
Allotransplant for Non-Malignant Diseases

- **Inherited metabolic disorders** - Adrenoleukodystrophy, Hurler syndrome, metachromatic leukodystrophy, osteopetrosis
- **Inherited immune disorders** - Severe combined immunodeficiency syndrome, Wiskott-Aldrich syndrome
- **Inherited red cell disorders** - Pure red cell aplasia, sickle cell disease, beta-thalassemia
- **Marrow failure states** - Severe aplastic anemia, Fanconi anemia
Inflammatory Cytokines

Pro-inflammatory
- Respond to tissue damage and microbial infection
  - Interleukin 1 (IL-1)
  - Interleukin 2 (IL-2)
  - Tumor Necrosis Factor (TNF)
  - Interferon gamma (INF-γ)
  - Interleukin 6 (IL-6)
  - Interleukin 8 (IL-8)
  - Interleukin 12 (IL-12)

Anti-inflammatory
- Suppress inflammatory response
  - Interleukin 10 (IL-10)
  - Interleukin 18 (IL-18)
The Role of Pro-inflammatory Cytokines

- Response to tissue damage and microbial infection
- Induce inflammation, fever, shivering, endogenous production of prostaglandins and corticosteroids, and growth of WBCs
- Release of IL-1, IL-2, TNF, IFNγ – initiating events in cytokine dysregulation
- Overproduction linked to neutropenic fevers and ES
- Circulating monocytes, macrophages and endogenous G-CSF upregulate IL-6, correlated with toxicities of HDT/ASCT
- Mediators such as endotoxins, IL-1 and TNF stimulate the production of IL-8
- IL-12 promotes differentiation of CD4+ T cells into Th1 cells, critical in inflammatory responses and neutrophil engraftment
Location of Centers Participating in the CIBMTR 2014

24-hour loop of worldwide air travel

Question – what do you need to get on an airplane?
Transplant Recipients in the US, by Transplant and Donor Type

- Autologous
- HLA-identical Sib
- Other relative
- URD+UCB

Transplants


* 2013 Data incomplete
Total Growth of the Be The Match Registry

Total Growth of the Be The Match Registry®

Source: National Marrow Donor Program/Be The Match FY 2014
Figure 2. Likelihood of Finding an 8/8 HLA Match by Year End, Based on Current Donor Availability and with Recruitment Trends Extended to 2017.

Projected match likelihoods for 2013 through 2017 (shaded area) were calculated on the basis of anticipated recruitment growth of 9% cumulatively each year.
Likelihood of Finding a Matching Adult Donor

SOURCE: National Marrow Donor Program / Be The Match 2013 fiscal year reports.
Transplants by Cell Source

Source: National Marrow Donor Program/Be The Match FY 2013
Transplants by Recipient Age

Source: National Marrow Donor Program/Be The Match FY 2014
Estimated Need

- Related transplants flat

- Unrelated transplants up 3 fold
  - HSCT for racial/ethnic minority groups up 4.5 fold
  - Transplants for over 50 up 8 fold
  - Transplants for over 65 up 12 fold
  - Incremental growth in all other decades of life
Top Patient Barriers to Transplant

- Language: 5% (First), 3% (Second), 2% (Third)
- Comorbidity: 77% (First), 22% (Second), 5% (Third)
- Housing: 38% (First), 36% (Second), 7% (Third)
- Psychosocial: 20% (First), 18% (Second), 5% (Third)
- Geography: 23% (First), 18% (Second), 8% (Third)
- Caregivers: 18% (First), 14% (Second), 12% (Third)
- Insurance: 89% (First), 29% (Second), 3% (Third)

National Marrow Donor Program
Be The Match
Top barriers to program growth

- Lack of patients: 17%
- Lack of providers: 25%
- Lack of space: 23%
- Reimbursement issues: 28%
- Internal competition: 10%
- External competition: 10%
- Lack of capital for expansion: 23%

First: 76%, 57%, 28%, 40%, 9%, 11%, 23%, 33%
Second: 9%, 23%, 28%, 21%, 10%, 10%, 23%, 11%
Third: 28%, 3%, 7%, 9%, 9%, 11%, 12%, 12%
Top staffing needs

- Physicians: 29% (Second) + 25% (First) = 54%
- Advanced Practice Professionals: 21% (Second) + 25% (First) = 46%
- Nurses: 19% (Second) + 22% (First) = 41%
- Other (pharmacy, lab personnel, data managers, BMT administrators): 26% (Second) + 31% (First) = 57%
One-year Survival by Year of Transplant, Donor and Age, Worldwide

Acute Leukemia, CML or MDS early disease status.
# Unrelated Transplantation Survival Over Time

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Survival Rate</th>
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<tbody>
<tr>
<td>2000 – 2004</td>
<td>48.5%</td>
</tr>
<tr>
<td>1996 – 2001</td>
<td>42.2%</td>
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</tbody>
</table>

*Source: Data and analysis on NMDP-facilitated transplants through CIBMTR®, the research arm of the NMDP.*
Role of Cord Blood in Transplants by Patient Race

- **Black/African American**: 44% Cord Blood, 56% Bone Marrow or Peripheral Blood
- **American Indian/Alaska Native**: 29% Cord Blood, 71% Bone Marrow or Peripheral Blood
- **Native Hawaiian/Other Pacific Islander**: 60% Cord Blood, 40% Bone Marrow or Peripheral Blood
- **Asian**: 25% Cord Blood, 75% Bone Marrow or Peripheral Blood
- **White**: 14% Cord Blood, 86% Bone Marrow or Peripheral Blood

Source: National Marrow Donor Program/Be The Match FY 2013
Role of Cord Blood in Transplants for Patients of Hispanic or Latino Ethnicity

Source: National Marrow Donor Program/Be The Match FY 2013
Transplants for Minority and White Patients

*Does not include Hispanic/Latino ethnicity

Source: National Marrow Donor Program/Be The Match FY 2013
Transplants for Minority Patients by Cell Source

Source: National Marrow Donor Program/Be The Match FY 2013
100-day Mortality after Unrelated Donor Transplants, 2010-2011

- Early Disease
- Advanced Disease
- Accelerated Phase
- Intermediate Disease
- Chronic Phase
- Blast Phase
- Other

Mortality, %

AML
ALL
CML
MDS/MPS
Aplastic Anemia
Immune Deficiency

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CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
Summary

• HCT is an exciting field of practice, clinical and scientific inquiry
• Ongoing advances offer this potentially life saving therapy to more individuals
• Cord Blood Transplantation offers life saving therapy to individuals who otherwise would not have a donor stem cell source
• Capacity – workforce and systems – remain a challenge to deliver transplant care
I believe everything was explained thoroughly and explicitly. But I don’t think that when you face a last option to be able to live that you process it. You hear, understand and acknowledge it but only when you are on the other side of transplant you allow your mind and heart to process that it basically cost everything you own. When hope reappears, you process it because then you have a value to balance it against.