BMT-CN Review Course

Basic Concepts and Indications for Transplantation

How the Experts Treat Hematologic Malignancies

Las Vegas, NV, March 10, 2016

David Rice, PhD, RN, NP
Director, Professional Practice and Education
Disclosures

No Disclosures
Objectives

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

Note: the primary reference source for this course is Ezzone, S. (2013) *Hematopoietic stem cell transplantation: a manual for nursing practice*. Oncology Nursing Society, Pittsburgh, PA
Normal Hematopoiesis

Blood stem cell

Myeloid stem cell

Myeloblast

Granulocytes
- Eosinophil
- Basophil
- Neutrophil

Red blood cells

Platelets

Lymphoid stem cell

Lymphoblast

White blood cells
- B lymphocyte
- T lymphocyte
- Natural killer cell
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.
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 bone marrow infused in victims of a nuclear reactor accident
- 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
  – Total Body Irradiation in dogs
    • Single dose fatal
    • Fractionated doses tolerated and dogs engrafted
  • Continued problems with graft failure and GVHD
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.
1968 Canine Long-Term Survivors
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
COH 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
<table>
<thead>
<tr>
<th>Center Code</th>
<th>Center Name</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>Beth Israel Deaconess Medical Center</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>50</td>
<td>Cedars Sinai Medical Center</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>52</td>
<td>Children's Hospital of Oakland</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>53</td>
<td>Fairfax Northern Virginia Hospital</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>56</td>
<td>Texas Tech University Medical Center</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>58</td>
<td>Charleston Hematology Oncology</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>59</td>
<td>Fred Hutchinson Cancer Center</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>60</td>
<td>Shands Healthcare &amp; University of Florida</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>61</td>
<td>University of Iowa Hospital &amp; Clinics</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>63</td>
<td>Johns Hopkins Oncology Center</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>64</td>
<td>Masonic Cancer Center University of Minnesota</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>65</td>
<td>Cleveland Clinic</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>68</td>
<td>University of Pittsburgh Medical Center</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>69</td>
<td>University of Wisconsin Hospital and Clinics</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>70</td>
<td>Froedtert &amp; Medical College of Wisconsin</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>71</td>
<td>Indiana University Hospital/Riley Hospital for Children</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>73</td>
<td>Karmanos Cancer Institute</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>74</td>
<td>All Children's Hospital</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>76</td>
<td>Children's Hospital of Los Angeles</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>78</td>
<td>Dana Farber Cancer Institute at Brigham and Women's Hospital - Adults</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>79</td>
<td>University of California - San Francisco - Pediatrics</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>80</td>
<td>Vanderbilt University</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>81</td>
<td>City of Hope National Medical Center</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>85</td>
<td>MD Anderson Cancer Center</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>86</td>
<td>Baylor University Medical Center</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>87</td>
<td>University of Louisville Hospital/James Brown Cancer Center</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>88</td>
<td>Virginia Commonwealth University Massey Cancer Center BMT Program</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
</tr>
</tbody>
</table>
Normal Hematopoiesis

Blood stem cell

Myeloid stem cell

Myeloblast

Granulocytes
- Eosinophil
- Basophil
- Neutrophil

Red blood cells

Lymphoid stem cell

Lymphoblast

B lymphocyte

T lymphocyte

Natural killer cell

Platelets

White blood cells
Immunology of transplantation

- Pluripotent
  - Able to self-replicate, proliferate and differentiate
    - Myeloid
      - RBCs, Platelets, WBC, Neutrophils, Macrophages
    - Lymphoid
      - T and B lymphocytes, Natural Killer Cells, Dendritic cells
- Ability to undergo self renewal or apoptosis (cell death)
- 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
Hematopoiesis – bone marrow microenvironment

- Begins in fetal yolk sac by eight days of conception
- After birth, bone marrow takes over this function
  - Adults have active bone marrow sites in the pelvis, vertebrae, ribs, sternum, and long bones of the humeri and femora
  - Bone marrow produces ~ 6 billion cells / kg of body weight / day
- Microenvironment
  - Bone cells
  - Vasculature
  - Stromal cells – produce cytokines that slow or speed cell growth
  - Extracellular matrix
Hematopoietic Stem Cells

• Predominantly found in BM
• Some found in peripheral blood
• Flow cytometry
  – Identifies proteins or protein clusters on cell surfaces
• CD34+ antigen (Calla Derived; Cluster Differentiation)
Organs of the Immune System

- Bone marrow
- Thymus – maturation of T lymphocytes (involutes with age)
- Spleen - “screens” blood for foreign substances
- Lymphoid tissue – provides immune cell transport
  - Lymph nodes
  - Appendix
  - Tonsils
  - Adenoids
  - Peyers patches
Cells of the Immune System

• Myeloid progenitors
  – Granulocytes,
  Erythorocytes,
  Monocytes,
  Megakaryocytes
• Mature neutrophils and monocytes
  – Non-specific immunity
  – Circulate, enter tissue as macrophages
    • Phagocytosis
    • Present foreign invaders to T and B lymphocytes
• Lymphoid progenitors
  – B lymphocytes secrete antibodies
  – Humoral (specific) immunity
  – T lymphocytes responsible for cellular immunity
    • Regulatory T cells (suppressor)
    • Cytotoxic T cells – activate other immune cells
    • Natural Killer (NK) cells
Goals of Therapy – Malignant and Nonmalignant disease

• Curative intent for many cancers after treatment of the disease
  – Often used in relapsed or refractory disease
  – May be part of upfront treatment plan
• Anti-tumor effect of Graft-versus-tumor (GVT), also called Graft-versus-leukemia (GVL)
• Used to suppress tumor growth in multiple myeloma
• Clinical trials investigation in connective tissue disorders and some nonmalignant hematologic disorders
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
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
- **Connective tissue disorders** – Systemic lupus erythematosus, juvenile rheumatoid arthritis, scleroderma
Pediatric HCT – Autologous and Allogeneic

**Autologous**

**Solid tumors**
- Neuroblastoma
- Medulloblastoma
- Sarcomas
- Recurrent Wilm’s tumor  
  – *Rescue therapy for cyclic chemotherapy*

**Hematologic malignancies**
- Hodgkin lymphoma
- Non-Hodgkin lymphoma

**Allogeneic**

**Hematologic malignancies**
- Acute myeloid leukemia
- Acute lymphoblastic leukemia
- Juvenile myelomonocytic leukemia
- Chronic myeloid leukemia
- Non-Hodgkin lymphoma
- Myelodysplasia
Pediatric HCT - Allogeneic

**Hematologic disorders**
- Sickle cell disease
- Fanconi’s anemia
- Thalassemia
- Severe aplastic anemia

**Immunodeficiencies**
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome

**Genetic disorders**
- Hurler’s syndrome
- Gaucher’s disease
- Adrenoleukodystrophy
- Krabbe’s disease
Indications for Hematopoietic Stem Cell Transplants in the US, 2012

- **Allogeneic (Total N=7,554)**
- **Autologous (Total N=11,145)**

Number of Transplants

- Myeloma/PCD
- AML
- ALL
- CML
- NHL
- HD
- MDS/MPD
- CLL
- Aplastic Anemia
- Other Non-Malignant Disease
- Other Cancer
Role of the Caregiver – Caregiver Burden

- Cancer is a significant stressor
- Transplant trajectory is uncertain
- Multiple episodes requiring constant adjustment
- Transplant care is harder than any other cancer caregiving
- High symptom severity
- More than 40 hours a week
- Long duration of care giving

Bevans & Sternberg, 2016
Caregiver Characteristics

• Spouse is usually the main caregiver
• Care is 24/7
• Varied “family” caregivers with different levels of involvement
• Affect on caregiver’s physical and psychological health
  – Immune issues
  – Coronary heart disease
  – Early death
• High demand of care may continue 1-6 years after transplant
• Most are novices at care giving