Hematopoietic Stem Cell Transplant

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Objectives

- Define HSCT
- Provide overview of HSCT process
- Discuss acute complications of HSCT
- Discuss chronic/late complications of HSCT

Indications for HSCT

- Malignant diseases:
  - Acute and Chronic Leukemia
  - Hodgkin’s Disease and Non-Hodgkin’s lymphoma
  - Myelodysplastic Syndromes
  - Multiple Myeloma
  - Selected solid tumors

- Non-malignant diseases:
  - Hematologic Disorders (Aplastic Anemia, Fanconi’s Anemia, Sickle Cell Anemia)
  - Congenital Immunodeficiencies (SCID, Wiskott Aldrich Syndrome)
  - Inborn Errors of Metabolism (Hurler’s Syndrome, Gaucher Disease)
  - Autoimmune Diseases (ex: Systemic Sclerosis, Multiple Sclerosis)

Approaches to Transplant

- Autologous
- Standard allogeneic
  - related or unrelated
- Non-myeloablative (allogeneic)

- Tandem
- Syngeneic
- Haploidentical
### Stem Cell Sources

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<thead>
<tr>
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<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td><strong>Bone Marrow (BM)</strong></td>
<td>Good source of stem cells</td>
<td>Anesthesia &amp; surgical risks for donor</td>
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<td></td>
<td>Lower rate of infections day + 100 to +365</td>
<td>Longer time to engraftment than PBSC</td>
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<td><strong>Peripheral Blood (PBSC)</strong></td>
<td>Most abundant source of stem cells</td>
<td>Long-term effect of growth factors on healthy donors unknown</td>
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<td>Faster Engraftment</td>
<td>Slightly higher risk of aGVHD &amp; cGVHD</td>
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<td>Lower rate of infections to Day +100</td>
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<td>More graft versus leukemia effect than BM or UCB</td>
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<td><strong>Umbilical Cord Blood (UCB)</strong></td>
<td>Readily available &amp; lower costs HLA mismatch more acceptable</td>
<td>Delayed engraftment</td>
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<td></td>
<td>Less risk of GVHD</td>
<td>Smaller “dose” of stem cells</td>
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### Autologous HSCT: An Overview

- **Theory behind therapy:** The stem cell “rescue” of the ablated marrow allows for high dose chemo/and or radiation to treat the disease.
- **Approach often utilized for certain types of lymphomas, multiple myeloma, selected solid tumors and non-malignant conditions**
- Requires collection and cryopreservation of one’s own stem cells
- Small risk of autologous GVHD, aka “pseudo-GVHD”

### Autologous HSCT: Mobilization and Apheresis

- **Mobilization:** A technique used to increase the number of circulating hematopoietic stem cells from the bone marrow into the bloodstream
  - High dose chemotherapy + G-CSF ± plerixafor
  - G-CSF
- **Apheresis:** The method for stem cell collection using a dialysis-type machine with cell separators that are programmed to collect stem cells

### Allogeneic HSCT: An Overview

- **Theory behind Therapy:**
  - **Standard allogeneic:** The stem cell “rescue” of the ablated marrow and “re-set” of the immune system by the donor’s stem cells allows for a combination of the chemotherapy and/or radiation therapy plus the stem cells that create a graft versus tumor effect to cure the disease.
  - **Nonmyeloablative allogeneic:** The donor stem cells provide a graft versus tumor effect that cures the disease.
Allogeneic HSCT: An Overview

- More common approach for acute leukemias. Also utilized to treat various hematological and immunological disorders, lymphomas, multiple myeloma, selected solid tumors
- Non-self source of stem cells: sibling, family member, unrelated donor, umbilical cord blood
- Immunosuppression necessary to prevent graft rejection and GVHD

HSCT Process

1. Planning phase
2. Preparing for transplant
3. Conditioning
4. Transplant
5. Awaiting Engraftment
6. Post-engraftment recovery
7. Long-term follow-up

Planning Phase

- Patient & Donor Planning
  - Oncologist reviews transplant with patient & family
  - Referral to transplant center for consultation
  - Address fertility
  - HLA type patient & siblings
  - Search the donor registries
- Other Preparations
  - Assess finances (insurance coverage or pay cash)
  - Select transplant center (statistics on NMDP website)
  - Select a caregiver
  - Make plans for relocation if necessary

HLA Typing

Degree of compatibility between donor and patient

- Minimum match recommendations:
  - 6/8 loci for PBSC and BM donors
  - 4/6 loci for UCB
- 25% chance that each sibling will be an HLA-match
- 70% of people do not have suitable family donor
- Median search time for a PBSC or BM donor is 51 days, and 2 weeks for UCB
Preparative Phase

- **Medical Evaluation**
  - Blood Work, Bone Marrow Aspirate & Biopsy, Lumbar Puncture, CT, PET, MRI
  - Oral exam and gynecologic exam
  - Nutritional, Psychosocial, and Spiritual Assessment
  - Chest X-ray, PFTs and Cardiac Studies

- **Family Conference & Informed Consent Process**
  - Discussion of protocol and plan, risks and benefits
  - Sign consents

- **Preparation of the Family and Caregiver**
  - Orientation to center; Caregiver classes & support groups

- **Central Line Placement**

Conditioning

- **Chemotherapy**
  - Myeloablative
  - Myelosuppressive

  Common Drugs: Melphalan, Fludarabine, Cyclophosphamide, Etoposide, Busulfan

- **Radiation**
  - Total Body Irradiation
  - “Mini” TBI

Transplant

- Stem cell infusion administered like an RBC transfusion

- **Cryopreserved**
  - Preserved with DMSO
    - Can cause hemolysis
    - Causes garlic breath
  - Transfusion reactions

- **Fresh**

Awaiting Engraftment

- Nausea, Vomiting, Diarrhea

- Mucositis
  - May effect the entire length of GI tract
  - May need PCA & TPN for some length of time

- Infections

- Hepatic Sinusoidal Obstruction Syndrome (SOS)
  - Risk factors include TBI, Cytoxan, prior liver disease
  - Can be fatal

- Engraftment syndrome
  - Fever and rash presents around time of engraftment, resembles GVHD
Allogeneic HSCT: Post Engraftment Recovery

- Patients are closely followed at the transplant center for several months
  - Acute GVHD and infection are major concerns
  - Seen daily to once/week for medical evaluation and blood tests
  - Nursing management of symptoms
  - Infusion therapy as needed
  - At day +80, patients are completely evaluated for disease state and complications and prepared for discharge home

Graft vs. Host Disease (GVHD)

- Donor T lymphocytes (the graft) recognize the antigens and cells in the transplant recipient (the host) as foreign and mount an immunologic attack

- Three conditions must be present
  - Graft must have sufficient number of competent cells
  - Host must have antigens that are not present in the graft
  - Host must be incapable of mounting an effective response to destroy the transplanted cells

Predictive Factors for aGVHD

- Donor/Host Factors
  - HLA disparity
  - Sex mismatch (especially female to male)
  - Age of donor and recipient

- HSC Source
  - PBSC > BM > UCB

- Immunomodulation
  - Omission of adequate aGVHD prophylaxis
  - TBI recipients

Clinical Features of Acute GVHD

- Skin (most common)
  - Maculopapular rash, often beginning with palmar/plantar surfaces and extending to the face, abdomen and trunk
  - Sunburned appearance to desquamation and loss of skin integrity

- Gut
  - Profuse, watery diarrhea with anorexia, nausea and vomiting
  - Diarrhea with intestinal bleeding and crampy abdominal pain to ileus

- Liver
  - Elevated alkaline phosphatase and bilirubin
  - RUQ pain, hepatomegaly and jaundice to ascites and encephalopathy
Prevention of aGVHD
- Highest degree of histocompatibility from donor (when multiple donors are available)
- Prophylactic immunosuppression with methotrexate, cyclosporine, mycophenolate mofetil, tacrolimus alone or in combination
- Selective T-cell depletion

Treatment of aGVHD
- Primary Therapy
  - Prednisone 1-2mg/kg/day followed by taper after response (may be given as IV methylprednisone)
- Secondary Therapy
  - Monoclonal antibodies
  - ATG
  - Sirolimus
  - PUVA (skin) or ECP (skin, liver and gut)

Prognosis of aGVHD
- Predicted by grade of aGVHD and response to initial therapy
- Poor responders to treatment have a high-risk of non-relapse mortality rate by one year

Allogeneic HSCT: Long-term Follow-Up
- Follow guidelines from transplant center about safe living with impaired immune function
- Late complications
  - Chronic GVHD
  - Late infectious complications
  - Pulmonary complications – Bronchiolitis obliterans, pulmonary fibrosis
  - Neurological complications
  - Psychological complications
  - Cataracts
  - Sexual disorders (ex: dry vaginal mucosa) and impaired fertility
  - Orthopedic complications – Fragile joints due to steroids
  - Secondary malignancy
Infections and HSCT

- **Pre-engraftment**: HSV, gram negative bacilli, staphylococcus epidermidis, GI-tract streptococci, candida, aspergillus
- **Early Engraftment**: candida, staphylococcus epidermidis, aspergillus, CMV, pneumocystis jiroveci
- **Late Phase**: CMV, VZV, encapsulated bacteria, aspergillus, pneumocystis jiroveci

Immune reconstitution after HSCT

- Innate immunity usually returns by day 100
- Adaptive Immunity:
  - CD4+ helper T-cells numbers may take months to return to normal levels
  - Serum immunoglobulins may take months to years normalize and gain full functionality
  - Immunosuppressants and chronic GVHD further impair immune reconstitution

Chronic GVHD

- Chronic graft versus host disease (cGVHD) is a syndrome caused by donor immune competent T cells recognizing and mounting an immune response against host cells which differ by histocompatibility antigens
- Resembles autoimmune or collagen vascular disorder

Predictive factors for cGVHD

- Previous aGVHD
- PBSC
- Older donor or recipient
- HLA disparity
Clinical Manifestations of Chronic GVHD

- Oral Symptoms
- Skin
- Nails
- Scalp & Body Hair
- Eyes
- Genitalia
- GI Tract
- Liver
- Lung
- Muscles/Fascia/Joints
- Hematopoietic/Immune

Treatment of cGVHD

- **Primary**
  - Prednisone 1mg/kg/day with a slow taper after improvement usually in combination with:
    - Daily cyclosporine or
    - Daily tacrolimus

- **Salvage**
  - Methotrexate
  - Mycophenolate Mofetil
  - Sirolimus
  - Tacrolimus
  - Azathioprine
  - Infliximab
  - Pentostatin
  - PUVA (cutaneous aGVHD)
  - ECP (cutaneous and liver aGVHD)

Supportive Care in cGVHD

- Infection prophylaxis
- Symptom palliation
  - Manage dry skin and protect from sun
  - Artificial tears
  - Oral care
  - Gynecology consult
- Nutritional intervention
- PT and OT
- Massage
- Psychosocial support

Prognosis of cGVHD

- Mortality in cGVHD is largely attributed to infection.

- Major morbidity is often present with extensive chronic GVHD and requires long-term therapy.
Factors influencing HSCT Outcomes

- Type of disease
- Disease status at time of transplant
- Co-morbidities
- Severity of GVHD

Web resources for outcome statistics:
- www.bmtinfonet.org
- www.marrow.org
- www.cibmtr.org

Summary

- HSCT indicated for a variety of malignant and non-malignant conditions, may be only potentially curative option for some conditions
- Major risks associated with HSCT in the acute and late phases are infection and GVHD
- Management of treatment side effects for transplant survivors can persist for years

Resources:

- National Marrow Donor Program
  www.marrow.org

- “Understanding Cancer” topics
  www.cancer.gov

- Seattle Cancer Care Alliance
  www.seattlecca.org

Questions?

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References


http://www.bbmt.org/article/PIIS1083879105006312/fulltext