Hematopoietic Stem Cell Transplant

Karen Anderson, MN, RN, OCN, BMTCN
Seattle Cancer Care Alliance

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 lymphoma and Non-Hodgkin’s lymphoma
  - Myelodysplastic Syndromes
  - Multiple myeloma
  - Selected solid tumors

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

Approaches to Transplant

- Autologous
- Allogeneic
  - Related or Unrelated
  - Myeloablative
  - Non-myeloablative
### Stem Cell Sources

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow</td>
<td>Good source of stem cells</td>
<td>Anesthesia &amp; surgical risks for donor</td>
</tr>
<tr>
<td></td>
<td>Less risk of cGVHD</td>
<td>Longer time to engraftment than PBSC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased risk of graft failure</td>
</tr>
<tr>
<td>Peripheral Blood</td>
<td>Most abundant source of stem</td>
<td>Growth factors given to healthy donors</td>
</tr>
<tr>
<td></td>
<td>cells</td>
<td>Higher risk of cGVHD</td>
</tr>
<tr>
<td>Umbilical Cord Blood</td>
<td>Readily available</td>
<td>Delayed engraftment</td>
</tr>
<tr>
<td></td>
<td>HLA mismatch more acceptable</td>
<td>Smaller “dose” of stem cells</td>
</tr>
<tr>
<td></td>
<td>Lack of donor risks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less risk of GVHD</td>
<td></td>
</tr>
</tbody>
</table>

### Autologous HSCT: An Overview

**Rationale for Therapy:**

High doses of chemo and/or radiation are given to treat the disease. The patient's own stem cells "rescue" the ablated bone marrow.

### 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

**Rationale for Therapy:**

- **Standard allogeneic:** High doses of chemotherapy and/or radiation are used to treat disease. The stem cell infusion “rescues” the ablated marrow. Also provides a graft versus malignancy effect.
- **Nonmyeloablative allogeneic:** Chemotherapy and radiation are given at lower doses that are immunosuppressive and myelosuppressive. The donor stem cells provide a graft versus malignancy effect.
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
  — Transplant center consultation
  — Address fertility now, if possible
  — 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

• Important HLA markers for HSCT are A, B, C, & DRB1
• Matched or mismatched donor options
• 25% chance that each sibling will be an HLA-match
• 70% of people do not have suitable family donors

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

Chemotherapy drugs listed w/ exception of busulfan are used off-label for transplant conditioning

Transplant

- Stem cell infusion administered like a blood product 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

- Graft Failure

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

  - Management of symptoms
  - Infusion therapy

  - At approximately day +80, patients are completely evaluated for disease state and complications and prepared for discharge home
Acute 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.

Incidence ranges between 35-80%.

Predictive Factors for aGVHD

- **Donor/Host Factors**
  - HLA disparity
  - Parity of female donor
  - 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**
  - Anorexia, nausea and vomiting, early satiety
  - Diarrhea, intestinal bleeding and abdominal pain to ileus

- **Liver** (rare)
  - 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**
  - Methotrexate, cyclosporine, mycophenolate mofetil, tacrolimus, sirolimus

- **Selective T-cell depletion**

*Immunosuppressive drugs listed are used off-label*
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

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
- Vaccinations

### Chronic GVHD

Pathophysiology is poorly understood

- Immune dysfunction
  - T-cells
  - B-cells
  - Fibrotic changes
- Resembles autoimmune or collagen vascular disorder

### Predictive factors for cGVHD

- Previous aGVHD
- PBSC
- Older donor or recipient
- HLA disparity
- Incidence ranges between 30-70%

### Clinical Manifestations of Chronic GVHD

<table>
<thead>
<tr>
<th>Oral Symptoms</th>
<th>GI Tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Liver</td>
</tr>
<tr>
<td>Nails</td>
<td>Lung</td>
</tr>
<tr>
<td>Scalp &amp; Body Hair</td>
<td>Muscles/Fascia/Joints</td>
</tr>
<tr>
<td>Eyes</td>
<td>Hematopoietic/Immune</td>
</tr>
<tr>
<td>Genitalia</td>
<td></td>
</tr>
</tbody>
</table>
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
  – Rituximab
  – Infliximab
  – Pentostatin
  – ECP

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.bethematch.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.bethematch.org
- “Understanding Cancer” topics
  www.cancer.gov
- Seattle Cancer Care Alliance
  www.seattlecca.org

Questions?

Karen Anderson, MN, RN, OCN, BMT/CN
kcanders@seattlecca.org

References


References


References


