Introduction to BMT

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Outline

- Hematopoietic cell transplantation (HCT):
  - Terminology
  - Rationale
  - Indications
  - Logistics
  - Outcomes
  - Complications
  - Survivorship issues
HCT Terminology
HCT Types

- **Autologous HCT** (patients own HPCs)
- **Syngeneic HCT** (HPCs from identical twin)
- **Allogeneic HCT** (HPCs from a donor)

**Graft source**
- Peripheral blood stem cells
- Bone marrow

**Donor source**
- Related donor
- Unrelated donor
- HLA-matched sibling
- Haplo-identical
- HLA-matched unrelated
- Umbilical cord blood

**Conditioning**
- Myeloablative
- Reduced-intensity or non-myeloablative

* HPCs: Hematopoietic progenitor cells

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Fundamentals of HCT
Rationale for HCT

• Deliver sufficient chemotherapy ± radiation therapy to destroy tumor cells
• Provide an autologous or allogeneic source of hematopoietic progenitor cells to replace marrow
• Establish graft tolerance to prevent rejection of donor cells (allogeneic HCT)
• Provide immune effector cells to mediate graft-versus-tumor activity (allogeneic HCT)
HCT is Offered for High-risk Disorders

RISK OF RELAPSE

- High dose therapy
- Graft-vs-tumor effect

RISK OF TOXICITY

- Treatment-related morbidity/mortality
Graft-vs-Tumor Effect

- Allogeneic HCT - alloreactive response mediated by donor T-cells against host malignant cells
Graft-vs-Tumor Effect

Graft-vs-host disease and risk for relapse in 2,254 recipients of HLA-identical sibling HCT for AML CR1, ALL CR1 & CML CP1

GVT EFFECT

CML
CLL
Low gd NHL
AML
High gd NHL
ALL
Myeloma

MM Horowitz et al, Blood 1990
HCT Indications
Autologous HCT Indications

- Lymphoma (chemo-sensitive)
  - DLBCL
  - Hodgkin
  - Mantle cell
  - Follicular
  - T-cell
- Multiple myeloma
  - Amyloidosis
- Relapsed/refractory germ cell tumors
- Pediatric sarcomas and brain tumors
Allogeneic HCT Indications

- AML and ALL
  - High risk CR1
  - CR2+
- MDS, myelofibrosis
- CML
- Lymphoma (including CLL)
- Multiple myeloma
- Inherited metabolic/immune disorders
- Hemoglobinopathy (sickle cell disease and thalassemia)
Indications for HCT in the US, 2011

- Allogeneic (Total N=7,892)
- Autologous (Total N=12,047)

Number of Transplants

- Multiple Myeloma
- NHL
- AML
- ALL
- MDS/MPD
- CML
- Aplastic Anemia
- CLL
- Other Non-Malignant Disease
- Other Cancer
- HD
HCT Logistics
Autologous HCT Steps

1. Patient selection
2. BMT workup
3. HPC collection (mostly PBSC)
   - Mobilization using growth factors alone or chemotherapy + growth factors
   - PBSC collection by apheresis
4. Transplant hospitalization
   - Conditioning regimen
   - HPC infusion (day 0)
   - Post-transplant recovery
5. Outpatient supportive care
Allogeneic HCT Steps

1. Patient selection
2. Donor search
3. BMT workup
4. HPC collection from donor
   - Mobilization using growth factors + apheresis
   - Bone marrow harvest
5. Transplant hospitalization (some outpatient)
   - Conditioning regimen
   - HPC infusion (day 0)
   - Post-transplant recovery
6. Outpatient supportive care
Allogeneic HCT: Donor Selection
HLA Matching for Allogeneic HCT

• Major histocompatibility complex – cluster of genes on chromosome 6 that regulate immune system
  - Class I (A, B, C)
  - Class II (DP, DQ, DR)

• Inherited as haplotypes – 1 in 4 chance a sibling will be identical
  - 20-40% chance of finding a sibling donor
HLA Matched Donor

Balance between Graft-vs-host disease and Graft-vs-tumor effect

**Poor**
- Poor engraftment
- More GVHD
- Poor survival

**HLA MATCH**

**Good**
- Better engraftment
- Less GVHD
- Better survival
Donors for Allogeneic HCT

- **Allogeneic HCT**
  - HLA-identical sibling donor
    - 6/6 match at HLA A, B, DRB1
  - HLA-Matched unrelated donor
    - 8/8 match at HLA A, B, C, DRB1 (if possible, also on DQ)
    - Mis-matched unrelated donor
      - 7/8 match at HLA A, B, C, DRB1
    - Umbilical cord blood
      - 4-6/6 match at HLA A, B, DRB1; two units may be used to cell dose
    - Haploidentical donor
      - 4-7/8 match at HLA A, B, C, DRB1

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Hematopoietic Progenitor Cell Collection
Bone Marrow Collection

- HPCs aspirated directly from the bone marrow
- Lower T-cell content than PBSC
- No need for “mobilization”
- Target cell dose: >2 x 10^8 TNC/kg
- Performed in OR
PBSC Collection

- Need to mobilize hematopoietic progenitor cells
- Autologous patients
  - G-CSF ± plerixafor
  - Chemotherapy + G-CSF ± plerixafor
- Allogeneic healthy donors
  - G-CSF
- HPCs collected by apheresis
- Higher T-cell content than marrow
- Target cell dose: >5 x 10^6 CD34+/kg
Graft Source: PBSC vs. marrow

- **Autologous HCT**: PBSC preferred
  - Faster engraftment and better survival shown in RCT’s
- **HLA-identical sibling donor HCT**: PBSC preferred
  - Faster engraftment, less graft failure and better survival shown in RCT’s
- **Unrelated donor HCT**: PBSC = bone marrow
  - Less graft failure but more GVHD with PBSC – RCT showed no survival difference
- **Haploidentical donor HCT**: Bone marrow preferred
  - Most experience with marrow, PBSC may be acceptable
Conditioning Regimen
Conditioning Regimen

• Chemo ± total body irradiation given prior to transplant (HPC infusion)

• Autologous regimens
  - Eradicate disease
  - Always myeloablative

• Allogeneic regimens
  - Eradicate disease + achieve immune suppression
  - Can be myeloablative or reduced-intensity
Autologous Conditioning

HIGH DOSE CHEMOTHERAPY ± RADIATION

GRAFT-VS-TUMOR EFFECT

Mortality 1 – 5%

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Allogeneic Myeloablative Conditioning

- Reserved for young healthy patients
- Prohibitive risks of treatment related mortality in older/sicker patients

Mortality 15 – 40%
Allogeneic Reduced Intensity Conditioning

- Immunosuppressive ‘enough’ for donor cell engraftment
- Option for older/sicker patients

Mortality 10 – 25%
Transplant Outcomes
General Prognostic Factors

- Age
- Disease risk
- Disease status
- Performance status and comorbidities
- Donor source (allogeneic HCT)

For patients who need a transplant, outcomes are best if transplant occurs early in the disease course.
Survival After HLA-identical Sibling Donor HCT for AML, 2001-2011

- Early (N=7,319)
- Intermediate (N=1,936)
- Advanced (N=2,858)

P < 0.001

Years

Probability, %
Survival after Autologous HCT for Hodgkin Lymphoma, 2001-2011

![Graph showing survival rates for different groups: CR (N=3,199), Not in CR, sensitive (N=3,929), Not in CR, resistant (N=1,215). The graph indicates a statistically significant difference with P < 0.001.]
Transplant Complications
Early Complications (first 3-6 mos)

- Graft failure (allo HCT)
- Acute GVHD (allo HCT)
- Toxicity related to chemo/TBI
  - Mucositis
  - GI toxicity
- Hematologic
  - Thrombocytopenia
  - TTP
  - Anemia
- Immunodeficiency
  - Infections

- Organ toxicity
  - Cardiac (arrhythmia, pericarditis)
  - Pulmonary (pneumonia, ARDS)
  - Renal (acute renal failure)
  - Hepatic (sinusoidal obstruction syndrome)
  - CNS (seizures, encephalopathy)
  - Bladder (hemorrhagic cystitis)
Infections

**TIME**
- **Day 0**
  - Pre-engraftment
  - Neutropenia
  - Mucositis
  - Central line
- **Day 30**
  - Post-engraftment
  - Acute GVHD
- **Day 100**
  - Late
  - Chronic GVHD
  - Impaired cellular and humoral immunity
- **1 year**

**RISK FACTORS**

**BACTERIAL INFECTIONS**
- Gram-negative bacilli
- *Streptococcus viridans*
- *Staphylococcus & Enterococcus spp.*
- Encapsulated bacteria (*Pneumococcus, Meningococcus*)

**VIRAL INFECTIONS**
- Herpes-simplex virus
- Cytomegalovirus
- Epstein-Barr virus-related lymphoproliferative disease
- Varicella-zoster virus

**FUNGAL INFECTIONS**
- Candida spp.
- Aspergillus spp.
- *Pneumocystis jiroveci*
Late Complications (>6-12 mos)

- Chronic GVHD (allo HCT)
- Immunodeficiency
  - Infections
- Second cancers
  - MDS/AML (auto HCT)
  - PTLD (allo HCT)
  - Solid tumors (auto and allo HCT)
- QOL and psychosocial issues

- Organ toxicity
  - Ocular (cataracts)
  - Cardiac (CHF, CAD)
  - Pulmonary (interstitial fibrosis)
  - Renal (CKD)
  - Hepatic (iron overload)
  - CNS (cognitive decline)
  - Endocrine (hypothyroidism, hypogonadism)
Graft-Versus-Host Disease

• Acute GVHD
  - Early post-transplant
  - Skin, GI tract, liver involvement common

• Chronic GVHD
  - Late post transplant, autoimmune manifestations
  - Skin, GI tract, mucosal involvement common

• Predisposing factors
  - HLA match
  - Donor source

• Associated with greater immunosuppression, infections and high rates of morbidity and mortality
RESOURCES:
bethematchclinical.org
asbmt.org