Overview
Blood and Marrow Transplantation and Cellular Immunotherapy

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Pluripotent Stem Cell
- Progenitor of all blood cells, "uncommitted"
- Asynchronous division
- Self renewing
- Location
  - Marrow
  - Peripheral Blood
  - Umbilical Cord Blood
- Migratory/homing properties
  - Cord Blood takes longer to "home"

Indications for BMT
- Malignant diseases:
  - Acute and Chronic Leukemia
  - Hodgkin’s and Non-Hodgkin’s lymphoma
  - Myelodysplastic Syndromes
  - Multiple Myeloma
  - Amyloidosis
  - Selected solid tumors
    - Breast (rare)
    - Renal cell
    - Germ cell
    - Primary CNS
    - Neuroblastoma
- Non-malignant diseases:
  - Hematologic Disorders
    - Aplastic Anemia
    - Fanconi’s Anemia
    - Sickle Cell
    - Thalassemia
  - Congenital immunodeficiencies
    - SCID
    - Wiskott Aldrich Syndrome
    - Inborn Errors of Metabolism
    - Hurler’s Syndrome
    - Guacher Disease
    - Autoimmune Diseases
    - Systemic Sclerosis
    - Multiple Sclerosis

Stem Cell Sources

<table>
<thead>
<tr>
<th>stem cell source</th>
<th>advantages</th>
<th>disadvantages</th>
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| Bone Marrow      |  Abundance of stem cells in BM  
|                  |  Lower rate of infections days = 100 to 365  |  Anesthesia risk for donor  
|                  |  Post-operative pain for donor  |
| Peripheral Blood |  Faster neutrophil and platelet recovery  
|                  |  Faster immune reconstitution  
|                  |  Reduced treatment-related mortality  
|                  |  Lower rate of infections to day = 100  
|                  |  More GVL effect than BM or UCB  |
|                  |  Easier collection  |  Bone pain for donor  
|                  |  Slightly higher risk of GVL  |
| Umbilical Cord Blood |  More quickly available  
|                  |  Less risk of GVL  
|                  |  More "matches"  |  Slightly higher rate of early mortality  
|                  |  Cannot obtain more cells from donor  |
Theory behind Therapy: Autologous

- **Autologous/Syngeneic:**
  - Lethal doses of chemotherapy/radiation therapy if patient not supported
  - Patient’s own stem cells “rescue” the ablated marrow
  - Cure is chemotherapy/radiation, stem cells are supportive care
  - Patient does not require immunosuppression as Graft vs Host disease does not occur

Autologous Process

- Mobilization chemotherapy to collect cells
  - Standard chemotherapy + high dose filgrastim
- “Conditioning” chemotherapy at least 1 month later
- Infusion of stem cells
- Monitor for infection and “engraftment”
- Discharge to primary provider about Day +30

Theory behind Therapy: Allogeneic

**Myeloablative:**

- Lethal doses of chemotherapy/radiation if patient not supported
- Donor stem cells “rescue” the ablated marrow and provide a new immune system for a graft versus tumor effect
- Cure is both chemotherapy/radiation and stem cells and graft vs tumor effect

**Nonmyeloablative:**

- Lower doses of chemotherapy/radiation
- Cure is the stem cells and graft vs tumor effect, chemotherapy eliminates microscopic disease
- Also called Mixed Chimerism, Mini, Reduced Intensity
Theory behind Therapy: Allogeneic

- **Immunosuppression**
  - Cyclosporine, tacrolimus, Mycophenolate mofetil
  - Required to prevent Graft vs. Host Disease
  - NonMyeloablative and Haploidentical BMT will receive dual immunosuppression
  - NonMyeloablative: Cyclosporine/Tacrolimus and MMF
  - Haplo: Cyclosporine/Tacrolimus, MMF and Cyclophosphamide post transplant
- **Immunosuppression taper:**
  - Begins about Day +80 depending on BMT type
  - Stopped if GVHD symptoms occur
  - Eventually taper completely

Allogeneic Process

- Identify donor
- “Conditioning” chemotherapy for patient
- Filgrastim “mobilization” for donor
- Infusion of HPC
- Monitor for infection, symptoms of GVHD
- Discharge to primary provider about Day +100-120 depending on BMT type
**Conditioning Therapy**

- Preparing the body for Hematopoietic Cell Infusion
- Chemotherapy
  - Dosed based on body weight, not body surface area
  - Side effects intensified due to much higher doses
- Radiation Therapy
  - Total Body Irradiation (TBI)
  - Radiation-tagged monoclonal antibodies (I-131, Y-90)
- Starts 3-9 days prior to BMT infusion

**Infusion of Stem Cells (HPC)**

- Infusion can occur inpatient or outpatient
- Infused like a blood product
- Side effects similar to blood products
  - Pre-medicate if required with blood products
  - *Exception*: Cryopreserved cells (autologous products and cord blood units)
    - Hypersensitivity to DMSO preservative
    - Red cell lysis from freezing

**Acute Complications**

- Pancytopenia
- Infection
- Mucositis
- Acute Graft vs Host disease
  - Allogeneic recipients only

**Infection Prevention**

- Avoid ill people and crowds
- Avoid people who have received live vaccines
- No flowers in vases, planting, or decorative moss in plants
- No vacuuming or dusting
- Immunocompromised, NOT neutropenic, diet
  - Fresh fruits/vegetables okay
  - NO
    - Deli meats
    - Moldy cheeses, pepper jack cheese, mexican soft cheeses
    - Uncooked tofu, meat or seafood
    - Chili peppers
    - Miso
    - unpasteurized juices
Acute Graft vs Host disease:

**Allogeneic**
- An immunologic reaction to the transplanted HPCs classically occurring in the first 100 days post BMT involving the **skin**, **liver**, and **gut**.
- GVHD is one of the most frequent complications after allogeneic BMT.
- Incidence 30-70% in matched transplants.
- Major cause of morbidity and mortality after BMT.
- Mortality (direct or indirect) can reach 50%.

**aGvHD**

**Three-step process**

**Acute GVHD Symptoms**
- **Skin**: Maculopapular rash
- **Gut**:
  - Upper GI: Nausea and vomiting, early satiety
  - Lower GI: Diarrhea
- **Liver**: Elevated bilirubin, cholestasis
Long Term Complications: Infection
- Prolonged neutropenia and immunosuppression greatest risk
- Bacterial
- Fungal
- Viral
  - HSV
  - VZV (shingles)
  - Cytomegalovirus (CMV): may require weekly monitoring for CMV titers depending on BMT source or type
- Includes viruses previously vaccinated against: revaccinate patient 1 year after BMT or after off all immunosuppression

Long-Term Complications: Auto and Allo
- Neurologic
  - Learning disabilities
  - Cognitive dysfunction
- Endocrine
  - Diabetes
  - Thyroid
- Sexual
  - decreased libido
  - delayed puberty
- Fertility
- Emotional

- Renal/Urinary
- Dental
  - Decreased salivary production
  - Gingivitis, Caries
- Relapse
- New malignancy
- Pulmonary
  - Pulmonary fibrosis
  - Bronchiolitis Obliterans
- Cardiac
  - Hypercholesteremia
  - CHF
  - Cataracts

Long-Term Complications: Allo
- Chronic GVHD
  - Skin
  - Liver
  - Gut
  - Oral
  - Ocular
  - Genital
  - Lung
  - Joints/Fascia
- Requires long term immunosuppression
- Skeletal (due to cGVHD)
  - Osteoporosis and osteopenia
  - Avascular necrosis

BMT Outcomes
- Full recovery from BMT
  - Complete remission
    - No long-term complications
      - life returns to normal
    - Few long-term complications
      - “new normal”
    - Multiple long-term complications
      - Poor QOL
      - Death
    - Relapse of Disease
      - Death
  - Partial recovery from BMT, death
New Frontiers in Research: Immune Effector Cells (IEC)

- BMT is the predecessor of current explorations in IEC
  - T-cells are non-specific in stem cell products

- Current Investigations: Tumor specific T-cells are collected, manipulated, and infused to “seek and destroy” cancer cells

- Commercially available products:
  - Kymriah: ALL for pediatric/adult < 25 years or subset DLCBC Lymphoma
  - Yescarta: subset of DLCBC Lymphoma adults

Cellular Immunotherapy

- Immunotherapy: Enhancing the immune response
  - Augment immune response externally: IL-2, interferon
  - Modify T cell response

- TIL: Tumor Infiltrating Lymphocytes
  - Lymphocytes harvested from a tumor and expanded ex vivo
  - Not subject to normal immune response such as T regulation
  - May “see” cells that have mutated
  - May have other medication immunotherapies administered to augment response

- TCR/CAR: T cell receptor
  - Specific to CD antigens
  - Modified using lente or retro viruses

Key Principles of IEC

- Re-infused T-cells are a “living” therapy that can expand and act on cancer cells over time

- Targeted therapy usually derived from the patient’s own immune system

- Lymphodepletion prior to infusion improves persistence of T-cells


Preparing CAR T cells

- Lymphodepletion
  - T cell expansion
  - CAR expression
CAR T-cell Therapy: Cytokine Release Syndrome and Neurotoxicity

Background

- Genetically modified T-cells that express a chimeric antigen receptor (CAR) that bind to a target antigen on a tumor cell
- When the T cell CAR binds to the target antigen, it causes activation of the receptor and T cell signaling which promotes target (tumor) cell killing and T cell proliferation.
- During this process, a large variety of cytokines may be released from the T cells and accessory cells that
  - activate the immune system
  - increase number of immune cells (e.g., macrophage) and
  - support further CAR T cell expansion and anti-tumor activity.

Cytokine Release Syndrome (CRS)

- May result in fevers, cardiopulmonary instability, hematologic toxicity, and multiorgan failure
- Occurs in 1-21 days following administration of CAR T-cell product
- Risk factors:
  - higher disease burden
  - greater proliferation/expansion of the CAR-T cells,
  - higher dose level of infused cellular product,
  - concurrent infection or underlying inflammatory state

Cytokine Release Syndrome: Common Symptoms and laboratory findings
** CRS: Grading (ASTCT, 2018)**

- If a commercial T-cell product (Yescarta or Kymriah) was administered, package insert guidelines for management of CRS should be considered.
- Tocilizumab (IL-6 receptor agonist) is effective in reducing CRS symptoms.

** CRS: Additional Supportive Care**

- Constitutional symptoms, including fevers:
  - Work up for infectious causes and initiate antimicrobial therapy.
  - Acetaminophen may be used for fever management.
- Systemic steroids as needed.
- Cardiovascular management:
  - Aggressive intravenous bolus and vasoactive support.
- Coagulopathy management:
  - PRBC transfusion, platelet and cryoprecipitate support as needed.
- Respiratory symptoms:
  - Supplemental oxygen as needed for hypoxemia.
- Neurological checks every 4 hours with first sign of CRS.
  - Avoid medications that could lower seizure threshold. (i.e. meperidine for rigors).

**Neurological Toxicity (NT):**

- May result in encephalopathy, seizures or (rare) cerebral edema.
- May occur 1 day up to 8 weeks post infusion of CAR T-cell product.
- Patients must stay close to center for 30 days post administration.
- Patients should not drive for 8 weeks after infusion.
Neurotoxicity: Additional Supportive Care

- Neurological assessment every 4 hours with first sign of NT.
  - Avoid medications that could lower seizure threshold. (i.e. meperidine for rigors).
- Avoid medications which could alter mental status (i.e. benzodiazepines, sedatives, etc.)
- Steroids are treatment of choice for isolated Neurotoxicity
- Tocilizumab should not be given in the absence of Cytokine Release Syndrome.

Resources

- American Cancer Society [www.cancer.org], select “Treatment & Support > Treatment Types
- Center for International Blood & Marrow Transplant Research (CIBMTR): [www.cibmtr.org/referencecenter/slidesreports/usstats/pages]
- Fred Hutch Long Term Follow Up Guidelines: [https://www.fredhutch.org/en/treatment/long-term-follow-up/information-for-physicians.html]
- Leukemia and Lymphoma Society [www.lls.org]
- National Cancer Institute [www.cancer.gov], select “About Cancer > Treatments”
- National Marrow Donor Program [www.bethematch.org]

References