Hematopoietic Stem Cell Transplantation

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Objectives
• Understand different types of transplant
• Donor types, conditioning
• Understand the process of transplant
• Understand possible complications
• Understand survivorship issues

Bone marrow transplantation
• A treatment for hematologic malignancies, aplastic anemia, errors in inborn metabolism, hemoglobinopathies
• Involves high dose/intermediate dose chemotherapy followed by hematopoietic stem cell infusion.
• Historically, pt <55, however, now patients up to 75 years old will undergo transplant

Hematopoietic Stem Cell Properties
• Capable of Producing all Blood cell lines
• Capable of Self Renewal
• CD34 positive
• Live in the bone marrow
**What is a Hematopoietic Stem Cell**

**Hematopoiesis**

- **Principles auto transplant**
  - High dose chemotherapy with stem cell rescue
  - “More is better”
  - “Transplant” is autologous cells that help the bone marrow recover

- **Common diseases for autologous transplant**
  - Autologous
    - Multiple myeloma
    - Relapsed Hodgkins disease
    - DLBCL: relapsed refractory
    - Germ cell Tumors
    - Ewings Sarcoma

**Indications for Hematopoietic Stem Cell Transplants in the US, 2013**

- Allogeneic (Total N=8,197)
- Autologous (Total N=11,255)
Autologous Transplants

**The Autologous Transplant Process**
1. **Collection**
   - Bone marrow is collected from the patient’s bone marrow or blood.
2. **Processing**
   - Blood or bone marrow is processed in the laboratory to purify and concentrate the stem cells.
3. **Cryopreservation**
   - Blood or bone marrow is frozen to preserve it.
4. **Chemotherapy**
   - High-dose chemotherapy and/or radiation therapy is given to the patient.
5. **Reinfusion**
   - Purified stem cells are infused into the patient.

**Principles: Allo transplant**
- **Alternative names:**
  - Peripheral blood stem cell transplant
  - Hematopoietic stem cell transplant
  - Bone marrow transplant
- **Goals:**
  - Chemotherapy to eradicate disease
  - New blood making system
  - New immune system

**What to expect at a BMT appointment...**
- A very scary appointment!!
- Take notes
- Record if possible
- Take someone with you!!
How does transplant work

What happens?

The Holy Grail of Transplant

Sequence of events of bone marrow transplant

1. Identify donor
2. Pre-transplant testing
3. BMT
4. Immediate post-transplant
5. Long term follow up

Graft versus host disease
Graft versus leukemia and infection

Must live within 30-60 min of transplant center ~100 days and have caregiver

May take up to a couple months


http://download.thelancet.com/images/journalimages/1470-2045/PIIS1470204501004557.fx2.lrg.jpg

DONOR SELECTION: UNDERSTANDING HUMAN LEUKOCYTE ANTIGEN

Who can be donors?

- Siblings:
  - 25% chance of being a full match
  - 50% chance of being a half match

- Unrelated donors:
  - Chances of finding one dependent on ethnicity

How do we identify donors?

- Human Leukocyte Antigen
  - Discovered: in mice (1937), humans (1954)
  - Allows self to identify self
Standard donors

- Donors
  - Matched— 8/8 or 10/10 based on HLA testing
    - related donor
    - unrelated donor
  - Mismatched- 7/8 or 9/10
    - Unrelated

What if you DON’T have a donor?

- Haplo-identical: half matched parent, child, sibling
  - Pro: (almost) everyone has one, readily available, recent data suggests that they are equivalent to MRD/MUD
  - Con: Limitations in conditioning regimens

- Umbilical cord blood
  - Pro: Rapidly available
  - Con: Hard to get adequate cell dose, expensive,

Pre-transplant evaluation

- Past medical history
- Cardiac function (ECHO)—heart test
- Pulmonary function (PFTs)—breathing test
- Infectious disease markers – look for evidence of infection
- Disease status (disease dependent)
Conditioning - preparatory regimens

- Goals:
  - Suppress recipient immune system
  - Disease control
- Intensity:
  - Myeloablative: no immune reconstitution without stem cells
  - Non-myeloablative: immune reconstitution possible without stem cells
  - Reduced intensity: Delayed immune reconstitution without stem cells

Examples of conditioning regimens

- Myeloablative
  - Cytoxan-12 Gy TBI
  - Busulfan-cytoxan (4 days busulfan, 3.2 mg/kg daily)
  - Busulfan-fludarabine (4 days busulfan)
- Reduced intensity:
  - Melphalan/Fludarabine
  - Busulfan-fludarabine (2 days busulfan)
  - Cytoxan/Fludarabine/Rituxan
- Non-myeloablative
  - 2 Gy radiation
  - Fludarabine-2 Gy radiation

How do we pick

- Age
- Co-morbidities
- Disease
- Donor

STEM CELLS

Where do they come from??
Marrow harvest

Peripheral blood stem cell harvest

Post transplant considerations

• Followed 1-2x a week for first 100 days
  • Monitor for graft versus host disease
  • Monitor for infection
• Careful with diet
• Restrictions with activity
• Need CAREGIVER the first 100 days
Graft versus host disease prevention

- Standard combination:
  - Methotrexate
  - Calcineurin inhibitor (ie cyclosporine, tacrolimus)
- T cell depletion:
  - CD34 selection (selects out ONLY stem cells)
  - Anti-thymocyte globulin (Gets rid of cells that cause GVHD temporarily)
  - Alemtuzumab (gets rid of almost all immune cells)
- Other agents:
  - Mycophenolate mofetil (cellcept)
  - Sirolimus (Rapammune)

ACUTE GVHD

- Historically characterized by onset at <100 days post transplant
- Currently - symptom based diagnosis
  - Rash
  - GI symptoms- nausea, vomiting, diarrhea
  - LFT abnormalities
- Considered OVERLAP if also have diagnostic symptoms of chronic GVHD

Presentation

- Rash-
  - Mild erythema
  - Diffuse macules/papules
  - Erythroderma
  - Bullous lesions/blistering
- Can be confused with:
  - Drug allergy
  - Viral exanthem
  - Busulfan rash

Is GVHD helpful?

**Treatment**

- **First line:**
  - If mild - will start with topical treatment
    - Skin: steroid cream
    - Gut: non-absorbable steroids
  - If no response, or diffuse disease -
    - Start Prednisone 2 mg/kg in divided doses with rapid taper
  - If no response within 5 days - dealer’s choice
    - Mycophenolate mofetil (cellcept)
    - Sirolimus (Rapammmune)
    - Photopheresis
    - Clinical trial

**Chronic graft versus host disease**

- Historically defined as ANY GVHD that occurs > day 100
- Now defined by clinical features
  - Must have diagnostic features to have a formal diagnosis of chronic GVHD

**cGVHD: a polymorphous skin disorder**

- **Epidermal cGVHD**
  - Lichen planus-like
  - Papulosquamous
  - Ichthyosiform
  - Poikiloderma
  - Keratosis pilaris-like
  - Acral erythema

- **Dermal cGVHD**
  - Lichen-sclerosus-like
  - Dermal sclerosis

- **Subcutaneous cGVHD**
  - Subcutaneous sclerosis
  - Fasciitis

**Overlap syndrome + late onset acute**

- **Overlap**: Has any of the classic features, as well as acute features
  - Erythematous or maculopapular rash
  - Nausea and vomiting or diarrhea
  - Liver test abnormalities
- **Late onset acute**:
  - No diagnostic features of chronic GVHD
Infections

• Viruses
  • Influenza, RSV, CMV…
  • “Common cold”
  • “GI bug”
  • Viruses dormant in our body-- ie varicella (chicken pox), herpes
  • Best protection: Avoid sick people and crowds, wash hands

• Bacteria
  • Normal bacteria on skin and in gut can be very dangerous after transplant
Fungus and molds

• All over the natural world
• Need to avoid yard work/gardening

REMEMBER

• Even if you have a normal white blood cell count--
  • They do not work appropriately!
  • It is like having guns with no ammunition

Late effects by organ system

Why do complications occur

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• TBI
  • Damage to tissues with low repair potential
  • Fertility, hypogonadism
  • Growth and development
  • Thyroid dysfunctions
  • Dental

• Chronic GYHID
  • And Corticosteroids
  • Immune deficiency
  • Late infections
  • Cataract
  • Sjog syndrome
  • Osteoporosis
  • Necrosis of bone
  • Ang complications

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**Oral Complications**
- Conditioning can result in damage to salivary glands (especially total body irradiation)
- Chronic graft versus host disease can result in destruction of salivary glands
- Risks:
  - Dental caries
  - Squamous cell CA of the mouth
- Recommendations:
  - Dental exam every 6 mo

**Liver**
- GVHD of the liver
- Iron overload from blood transfusions
- Recommendations
  - Check liver enzymes yearly
  - Check ferritin, if greater than 2500, consider initiation therapeutic phlebotomy (one unit every 4-6 weeks if hct >38%) OR iron chelation

**Respiratory complications**
- Most patients will have some decline in pulmonary function
  - Normal population FEV1 declines by 1% per year
  - BMT patients can experience more rapid decline or post transplant lung complications
- Monitoring of lung function important

**Thyroid function**
- 20-40% will experience hypothyroidism
- Check thyroid tests in the blood yearly
Gonadal Dysfunction

- Very common after fully ablative conditioning
- High rates of infertility:
  - Men - 92%
  - Women - 99%
- More common after regimens containing TBI
- Most women are post menopausal

Recommendations:
- Screen for menopause in women
- Hormone replacement until age where naturally would go into menopause

When possible think about fertility preservation prior to transplant!!

Diabetes

- Many patients develop diabetes after transplant
- High incidence with steroid use
- Treatment goals similar to those of general population with diabetes

Bone Health

- Factors that influence bone health:
  - Hypogonadism (especially in females)
  - Medications: ie steroids,
  - Vitamin D deficiency

Recommendations:
- Bone density test at one year
  - If abnormal recheck as needed
- Bisphosphonate therapy

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Growth

- This is a problem in pediatric recipients of BMT
- If child doesn’t have appropriate growth velocity, will require work up for thyroid and growth hormone
Ocular Complications

- Patients with chronic GVHD can have dry eyes
- Long term steroid use or total body irradiation can cause cataracts
- Yearly visits with ophthalmology

Cardiovascular

- At a higher risk for metabolic syndrome
  - Dyslipidemia
  - Insulin resistance
  - Obesity
  - Hypertension

- Recommendations:
  - Yearly cardiovascular risk assessment

Recommendations for cancer screening

- Routine guidelines
  - Pap
  - Colonoscopy

- Unique for transplant patients:
  - In women who had TBI (as a child)- start screening at age 25 with mammograms
  - In women who had TBI (as an adult)- start screening 8 years out from radiation

Quality of life after transplant

- Physical and Functional well being
- Emotional
- Cognitive
Depression

• VERY common post transplant: at least 50% of patients will experience depression following transplant

• If at least half the days in the past 2-4 weeks someone experiences:
  • Little interest or pleasure in doing things
  • Hopeless, depressed, down or helpless
  • Other symptoms: sleeping issues, no energy, appetite changes, irritability


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Return to work

• 82% survivors returned to work at one year

Socializing

• 6 mo- 52% felt like socializing
• 1 year- 77% felt like socializing
• 2 years- 84% feel like socializing

What to expect 5 years out

- 80-90% better 
  - Appreciation for life
  - Life satisfaction
- 50-60% better 
  - Parenting/spouse role
  - Religious/spiritual life
- 20-35% better 
  - Work/student role
  - Home activities
- 5% worse 
- 10% worse

Conclusions

- Bone marrow transplant can CURE many diseases
- Long process— but worth it!
- Post-transplant health maintenance important
- There is a light at the end of the tunnel!!

Links

- BMTinfonet.org
- Strength Doesn't Come From What You Can Do
- National Marrow Donor Program
- Be the Match
- Support Bone Marrow Transplant
  - Survivors, Caregivers, Donors