Introduction to Graft-versus-Host Disease (GVHD)

Celebrating a Second Chance at Life
Survivorship Symposium

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LEARNING OBJECTIVES

• Differences between acute and chronic graft-versus-host disease
• Sites (Organs/tissues) typically affected by GVHD
• Incidence and typical onset of acute & chronic GVHD
• Therapies to prevent and treat acute & chronic GVHD
• Side effects of therapies used to treat GVHD
• Physical & Emotional challenges associated with GVHD
HOW DONOR STEM CELL TRANSPLANTS CURE CANCER

Donor Bone Marrow (Graft)  
Immune Cells  
Blood Stem Cells  
Transplant  
GVHD  
The Patient (Host)

THE TWO FORMS OF GRAFT-VERSUS-HOST DISEASE

• Acute Graft-versus-host disease
  • Typically occurs earlier after transplant
  • Primarily affects the skin, intestines and liver
  • Inflammatory Process
• Chronic Graft-versus-host disease
  • Typically does not occur until 2+ months after transplant
  • Can affect most parts of the body
  • Closely resembles autoimmune diseases
GVHD PREVENTION: GRAFT MANIPULATION

Graft Manipulation (modifying the transplanted cells)

- **T-cell depletion/CD34+ Cell Selection**
  - Removal of the immune cells that cause GVHD
  - Associated with increased infection risk, slow immune recovery
- **αβ-T-cell and B-cell Depletion**
  - Leaves γδ T-cells while removing other immune cells
  - Felt to improve risk for infections and relapse compared to T-cell depletion
- **Newer strategies being investigated**
  - Naïve T-cell depletion, ORCA-T grafts

GVHD PREVENTION MEDICATIONS: CYCLOSPORINE AND TACROLIMUS

Tacrolimus (Prograf, FK-506), Cyclosporine (Neoral)

- Immunosuppressive medicines, also used for solid organ transplant
- Typically Started before day of transplant, continued for 2-6 months
- Must monitor drug levels
- Can be harmful to kidneys
- Can cause low magnesium levels
- Cyclosporine can cause gum thickening and excess hair growth
GVHD PREVENTION MEDICATIONS: METHOTREXATE

• Chemotherapy agent used to treat cancer and autoimmune diseases
  • When used to prevent GVHD, given at autoimmune doses
  • Typically given on post-transplant days 1, 3, 6 ± 11
• Can worsen mouth sores from chemotherapy/radiation (mucositis)
• Cannot be given during time of liver injury
• Cannot be given if fluid collections (effusions or ascites) are present

GVHD PREVENTION MEDICATIONS: MYCOPHENOLATE

Mycophenolate Mofetil (MMF, CellCept, Myfortic)
• Typically started around time of transplant, continued for 1 month
• Can cause lower blood counts
• Can cause gastrointestinal symptoms
  • Nausea, Vomiting, Diarrhea
GVHD PREVENTION MEDICATIONS: SIROLIMUS

Sirolimus (Rapamycin)
• Can be used instead of Tacrolimus or Cyclosporine
• Also can be harmful to kidneys
• Drug levels must be monitored
• Can cause high triglyceride and cholesterol levels

GVHD PREVENTION MEDICATIONS: CYCLOPHOSPHAMIDE

• Typically given on days +3 and +4 after transplant
• Can cause nausea and vomiting
• Can cause bladder irritation/bleeding
  • Prevented with IV hydration and Mesna (IV medicine)
GVHD PREVENTION MEDICATIONS: ABATACEPT

• IV Medication given in 4 doses over 1st month of transplant
• Tends to be well tolerated
• May cause higher blood pressures

GVHD PREVENTION: COMMON STRATEGIES

• Tacrolimus/Cyclosporine/Sirolimus with:
  • Methotrexate (most common with matched related and unrelated donor transplantation)
  • Mycophenolate (common with cord blood transplantation)
• Cyclophosphamide + Tacrolimus + Mycophenolate
  • Commonly used with haploidentical (half-matched) transplant
  • Being more widely used following unrelated donor transplant
• Abatacept + Tacrolimus + Methotrexate
  • Used following mismatched unrelated donor transplant
  • Being investigated following matched unrelated donor transplant
ACUTE GVHD: INCIDENCE & TYPICAL ONSET

• Occurs in anywhere from 25-70% of patients depending on age, transplant type and risk factors
• Most often occurs between 2 weeks and 2 months post-transplant
• May occur later (6+ months after transplant)
• Can involve any combination of skin, intestinal and liver involvement

ACUTE GRAFT-VERSUS-HOST DISEASE: SKIN

• Most commonly involved site of acute GVHD
• Presents as a red rash
• Can be splotchy or more widespread
• When most severe (rare), can cause blisters or sloughing of skin
ACUTE GRAFT-VERSUS-HOST DISEASE: INTESTINES

- Acute Gastrointestinal GVHD: Divided into upper and lower GI GVHD
- Upper gastrointestinal acute GVHD
  - Constant nausea
  - Frequent vomiting
  - Loss of appetite with associated weight loss
- Lower Gastrointestinal acute GVHD
  - Watery diarrhea (typically 3+ episodes per day)
  - May have associated crampy pain
  - Severe pain and/or bloody stool at most severe

ACUTE GRAFT-VERSUS-HOST DISEASE: LIVER

- Least commonly involved site
- Presents with increased bilirubin on blood tests
- Clinically presents with jaundice
  - Yelllowing of eyes and skin, darker urine
  - Typically is painless
ACUTE GVHD: TREATMENT

- For mild skin GVHD (<50% body coverage)
  - Topical steroids
- For upper gastrointestinal GVHD
  - Can consider nonabsorbable oral steroids (budesonide and/or beclomethasone)
- For all others, systemic (Oral or Intravenous) steroids
  - Current clinical trials may add a second agent

Treatment is over weeks to months!

ACUTE GVHD TREATMENT: STEROIDS

- Typically started at twice daily dosing for 1+ week
  - If GVHD is improving, decrease dose fairly rapidly
- Side Effects
  - Weight gain (including “moon facies”)
  - Mood swings
  - High blood sugars
  - High blood pressures
  - Risk for infections
  - Bone health concerns (long-term effect)
ACUTE GVHD MEDICATIONS: SECOND LINE TREATMENT

- Ruxolitinib (Jakafi)
  - Oral medication given twice daily
  - Can cause low blood counts
- Extracorporeal Photopheresis (ECP)
  - Treatment procedure involving UV light therapy to collected immune cells
  - Typically given 2+ times per week initially, then spaced out
- Many clinical trials of other therapies underway
  - Mesenchymal Stem Cells, Hormones, New Medicines

CHRONIC GVHD: INCIDENCE AND TYPICAL ONSET

- Occurs in anywhere from 15-40% of patients depending on transplant type and risk factors
- Most often occurs between 4 months and 2 years post-transplant
- May occur sooner (2 months after transplant) or later
- Can involve any almost any body site and any combination of sites
CHRONIC GVHD: COMMON SITES

Eyes: Light sensitivity, Dryness, Tearing, Pain, Redness

Mouth: Redness, Sores, Bumps, Dryness, Sensitivity

Lungs: Shortness of Breath, Cough, Emphysema, Frequent Infections, Fluid Collections

Digestive Tract: Difficulty Swallowing, Food getting stuck, Choking, Constipation, Diarrhea

Skin: Thickening, Scarring, Stiffness, Dryness, Color Changes, Nail Changes

Genitals: Scarring, Irritation (Male), Scarring, Narrowing, Pain with Sex (Female)

Muscles/Joints: Limited Mobility, Cramping, Pain

Chronic GVHD: LESS COMMON SITES

Scalp: Thickening, Flaking, Hair Loss

Brain: Personality and Speech Changes, Seizures, Weakness, Confusion, Sleepiness

Heart: Fluid collection (pericardial effusion)

Kidneys: Kidney Injury, Foamy Urine (Protein loss)

Blood Counts: Low from immune destruction
CHRONIC GVHD: TOPICAL TREATMENTS

• **SKIN**
  • Topical steroid creams/ointments
  • Moisturizers
  • Other prescription creams/ointments (immunosuppressants, others)
  • UV Therapy

• **Mouth**
  • Steroid mouthwash
  • Light therapy (under investigation)

• **Eyes**
  • Artificial Tears
  • Other Prescription drops (steroids, immunosuppressant, others)

CHRONIC GVHD: LUNG TREATMENTS

• **FAM Therapy:**
  • Inhaled steroids (e.g. Fluticasone, Budesonide)
  • Azithromycin – One pill three days per week
  • Montelukast (Singulair®) – Daily pill (Allergy/Asthma Medicine)
CHRONIC GVHD: SYSTEMIC TREATMENT

- Always use Local/Topical therapies for affected sites
- First line treatment: Steroids (typically by mouth)
  - Lower starting dose than acute GVHD – 1-2 times daily
  - Treatment typically over several months
  - Same side effect risks as when used for acute GVHD

CHRONIC GVHD TREATMENT: BEYOND STEROIDS

- 3 Approved Medications for Chronic GVHD failing steroids
- Ibrutinib (Imbruvica®)
  - Approved for adults and children at least 1 year old
  - Once daily Pill/Liquid
  - Common Side Effects:
    - Nausea/Diarrhea
    - Fatigue
    - Bruising
    - Muscle spasms
    - Infections (e.g. Pneumonia)
BEYOND STEROIDS: RUXOLITINIB

- 3 Approved Medications for Chronic GVHD failing steroids
- Ruxolitinib (Jakafi®)
  - Approved for adults and children at least 12 years old
  - Twice daily pill
  - Common Side Effects:
    - Low Blood Counts
    - Infections

BEYOND STEROIDS: BELUMOSUDIL

- 3 Approved Medications for Chronic GVHD failing steroids
- Belumosudil (Rezurock®)
  - Approved for adults and children at least 12 years old
  - Once/Twice Daily Pill
  - Common Side Effects:
    - Nausea/Diarrhea
    - Fatigue
    - Liver irritation
    - Infections (e.g. viral respiratory infections)
BEYOND STEROIDS: OTHER TREATMENTS

- Extracorporeal Photopheresis (ECP)
  - Blood immune cell collection by machine
  - Treatment of immune cells with UV light
  - Cells given back by IV
  - Also used for acute GVHD
- Upcoming and experimental therapies
  - Axatilimab (clinical trial completed, promising results)
    - Given Intravenously every 2 weeks
    - Several other experimental treatments under investigation

GVHD: PHYSICAL CHALLENGES

- Medication Side Effects
  - Steroids (Weakness, Weight Gain)
- Chronic GVHD
  - Limited Mobility (Joint/Skin Tightness)
  - Fatigue
  - Limitations in Activity (Lung involvement)
GVHD: EMOTIONAL CHALLENGES

- Medication Side Effects
  - Steroids (Mood swings, sleep disruption)
- Body Image Issues
  - Hair Loss
  - Scarring/Rashes
  - Weight Gain/Acne from Steroids
- Limitations on work/school participation
- Chronic GVHD: Long Term Treatment
- Sexual Health

QUESTIONS?

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