Introduction to Graft-versus-Host Disease

Celebrating a Second Chance at Life Survivorship Symposium

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Introduction to Graft-versus-Host Disease (GVHD)

1. Donor cell transplant: a quick introduction
2. Mechanisms leading to GVHD
3. Incidence and risk factors for GVHD
4. Signs and symptoms of GVHD
5. Prevention of GVHD
6. GVHD treatment

Donor cell transplant

Recipient

“Host”

“Graft”

Human Leukocyte Antigen “HLA”

Matching

Donor
Source of cells for allogeneic stem cell transplant

Recipient
“Host”

Peripheral Blood Stem Cell
Bone Marrow Harvest
Cord Blood Unit

Potential donors for allogeneic stem cell transplant

Recipient
“Host”

In the Family:
Matched Sibling
Haploidentical

Volunteers:
Matched Unrelated
Cord Blood
What is the donor really donating?

Blood forming cells:
Replace host’s stem cells

Immune Cells:
Destroy cancer cells in the recipient
“Graft versus Leukemia”

Transplant: Unique way to treat blood cancers

“4 MUST”:
1. Recipient disease status
2. Recipient fitness status
3. Donor availability
4. Support system

IMMUNOTHERAPY: Graft versus Leukemia → CURE

LIFE CHANGING
Rejection

Host

Graft

Engraftment

Graft versus Leukemia

Graft versus Host Disease
**Allogeneic transplant: How to define success**

- Engraftment
- Cure the leukemia
- NO Graft versus Host Disease
- Provide immunity lifelong

**Tolerance**

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**Allogeneic transplant: General Schema**

- **Conditioning**
  - Prevent Rejection
  - +/- destroy cancer cells
- **Post Tx Immunosuppression**
  - Prevent GVHD
What is Graft-versus-Host Disease (GVHD)?

- **Biological consequence** of the transfer of a donor immune system into the recipient
- Immunosuppressive medications to prevent GVHD is necessary
- GVHD can be eliminated by removing immune cells (T-cells) from the donor collection

Graft-versus-host disease (GVHD)

- GVHD is associated with graft-versus-leukemia (GVL) effect
- Remove the donor T cells from transplant = increase risk of disease relapse
GVHD: How does it happen?

Chemo and radiation: Tissue damage
Damage to intestinal environment

Cytokines and inflammatory mediators

Donor immune cells discover host targets

Cells cross talk amplifies and directs fight in many directions

Issues in control and education the immune cells

Acute GVHD: three-step model

(1) INITIATION Phase:
- Chemo and radiation → inflammation
- Release of inflammatory substances

(2) ACTIVATION Phase:
Donor Immune cells
- “recognize” non self environment
- expand in number

(3) EFFECTOR Phase:
Donor immune cells attack tissues
Chronic GVHD: It gets complicated

- Tissue damage $\rightarrow$ Inflammation
- Damage to small vessels
- Donor B and T cells expand into an “aggressive subtype”
- Immune cells escape regulation: attack recipient organs
- Inflammation persists
- Activation of cells macrophages and fibroblast $\rightarrow$ Fibrosis
- Overproduction of antibodies that target body and deposit into organs

GVHD: Acute and Chronic

Acute GVHD

\[ \text{ACUTE} \\ \text{Inflammation} \]

Chronic GVHD

\[ \text{PROGRESSIVE} \\ \text{Chronic inflammation} \\ \text{Fibrosis: SCAR TISSUE} \]
GVHD: Acute and Chronic

- About 70% of patients get it
- Most commonly early after transplant (2-6 weeks), but can happen later too (past 3 months)
- Bad or life threatening in 10-15% of patients
- When happens the first treatment does not work in 30-40% of cases
- Leading cause of early post transplant death
### Acute GVHD: Risk factors

<table>
<thead>
<tr>
<th>Donor factors</th>
<th>Transplantation factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA Mismatched</td>
<td>Stem cell source {Blood &gt; Bone marrow &gt; cord blood}</td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>High cell dose</td>
</tr>
<tr>
<td>Sex mismatch {Woman → Man}</td>
<td>Pre-transplant chemo or radiation {more &gt; less intense}</td>
</tr>
<tr>
<td>If donor is a woman: number of pregnancies</td>
<td>Post-transplant immunosuppression combo</td>
</tr>
<tr>
<td>Older donor</td>
<td></td>
</tr>
</tbody>
</table>

### Organs affected by acute GVHD

- **Skin**: Rash
- **GI**: Diarrhea, No appetite, Nausea vomiting, Rapid weight loss
- **Liver**: Increased labs
Chronic GVHD

- Most serious and common long-term complication of transplant
- Occurs in 30% (young, sibling donors) to 70% (older, unrelated donors)
- Median time to development is 4-6 months after Transplant
- 50% of patients have 3 or more involved organs/tissues
- On average needs treatment for 2-3 years; 15% require therapy >7 years

Chronic GVHD: Risk factors

Previous history of severe acute GVHD

Donor factors

Same as acute GVHD

Transplant factors
Chronic GVHD: Review of symptoms

- **Skin feels tight or hard**, increased dryness, pruritus, or looks different (ie, new rash, papules, discoloration, shining scar-like, scaly)
- **Sweat glands**: Inability to sweat or to keep body warm
- **Loss of hair** (scalp or body including bows or lashes), or nail changes (ridges, brittle, loss)
- **Stiffness** or pain in the wrists, fingers, or other joints
- **Eye** dryness, sensitivity to wind or dry environments, pain

Adapted, Flowers & Martin Blood 2015
Chronic GVHD: Review of symptoms

- **Oral dryness**, taste alterations, sensitivities (spicy/carbonated drinks, toothpaste), ulcers/sores, pain
- **Foods or pills gets stuck** upon swallowing
- **Cough, dyspnea** (on exertion or rest) or wheezes
- **Vaginal dryness**, pain, dyspareunia (female); pain or dysuria due to stenosis of urethra (male)
- **Unexplained weight loss** or inability to gain weight

Adapted, Flowers & Martin Blood 2015

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cGVHD: Skin and deep tissues

- Lichen planus-like feature
- Lichen sclerosus-like
- Photosensitivity
- Keratosis plana
- Depigmentation
- Alopecia
- Dermal sclerosis
- Edema (early fascitis / early sclerosis)
- Deep Scleroderma
- Fasciitis
- Myositis

Adapted, Flowers & Martin Blood 2015
**cGVHD: Skin and deep tissues**

**Manifestations**
- Lichen planus-like feature
  - Lichen sclerosus-like
  - Dystrophia inveterata
- Keratoacanthosis
  - Depigmentation
- Alopecia
- Dermal sclerosis
- Edema (early fasciitis / early sclerosis)
- Deep Sclerosis
- Fasciitis
- Myositis

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**cGVHD: Eye, mouth, nails**
GVHD: Multiorgan disease

aGVHD

GI

Skin

Liver
cGVHD

Others (effusions...)

Mouth

Skin

Nails/Hair

Lung

Liver

Geriatric

Joint/Fascia

GVHD grading – Intro

GVHD: Multiorgan disease

0 No clinical manifestations/symptoms

1 Clinical manifestations with mild disability

2 Clinical manifestations with moderate disability

3 Clinical manifestations with severe disability

Chronic GVHD: Graded based on disability

Grading in each organ/system:

Mild

- 1 or 2 organs or sites (except lung) with score 1
  - Mild oral symptoms, no decrease in oral intake
  - Mild dry eyes, lubricant eyedrops ≤ 3x/day

Moderate

- 3 or more organs with score 1
- At least 1 organ or site with score 2
  - 19-50% body surface area involved or superficial sclerosis
  - Moderate dry eyes, eyedrops > 3x/day or punctal plugs
- Lung score 1 (FEV1 60-79% or dyspnea with stairs)

Severe

- At least 1 organ or site with score 3
  - > 50% body surface area involved
  - Deep sclerosis, impaired mobility or ulceration
  - Severe oral symptoms with major limitation in oral intake
  - Severe dry eyes affecting ADL
- Lung score 2 (FEV1 40-59% or dyspnea walking on flat ground)

2014 NIH Consensus
GVHD prophylaxis: planned immunosuppression

Tacrolimus or Cyclosporine +/- Sirolimus (rapamicyn)
+
Methotrexate or MMF

ATG
(Rabbit) antibodies vs T cells

GVHD prophylaxis: Planned immunosuppression

Tacrolimus or Cyclosporine +/- Sirolimus (rapamicyn)
+
Methotrexate or MMF
GVHD prophylaxis: Planned immunosuppression

**Tacrolimus + MMF**

**Cyclophosphamide (PTCY)**

GVHD treatment: principles

1. **Start treatment EARLY, LOCAL:**
   - supportive treatment + nonabsorbable steroids
   - Get a specialist involved

2. **Steroids: mainstay of Systemic Treatment**
   - Acute: 40-60% responds < 5 days
   - Chronic: **needed long course, combo not better**

3. **Steroids don’t work: always an issue**
   - Bad: always predict poor outcome
   - Good: **new drugs**
Organ specific treatment

- Skin: topical steroid, Tac, CSA, PUVA/UVB
- Oral: topical steroid, Tac, CSA
- Eye: ear drops, CSA eye drops, punctal occlusions, contact lenses, scleral lenses
- Lung: FAM
- Liver: Ursodiol
- GI: non absorbable steroids
- GU: topical steroid, Tac, CSA

Managing Chronic GVHD

- Goal: relieve symptoms; avoid progression to sclerosis, get LIFE BACK
- Therapy required for 2-3 years; 15% still require therapy >7 years

**Extended GVHD Team**

**Subspecialists**
- Oral medicine
- Ophthalmologist
- Dermatologist
- Gynecologist

**Supportive staff**
- Physical therapist
- Occupational therapist
- Nutritionist

**Psychosocial support (patient and caregiver)**
- Mental health counselors
- Back-to-work or job retraining resources
Managing Chronic GVHD

Systemic treatment
Once steroids fail or are not enough there is no optimal treatment choice

Treatment choices are based on:
- Cost and duration
- Logistics
- Toxicity
- Physician experience
- Available clinical trial

Table 6. Agents used for secondary treatment of chronic GVHD*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Overall response</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP (Photopheresis)</td>
<td>65-70</td>
<td>70%-78% at 1 y</td>
</tr>
<tr>
<td>Rituimab</td>
<td>66-86</td>
<td>72% at 1 y</td>
</tr>
<tr>
<td>Imatinib</td>
<td>22-79</td>
<td>75%-84% at 1.5 y</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>53-56</td>
<td>34%-60% at 1-3 y</td>
</tr>
<tr>
<td>Mesenchymal stem cells</td>
<td>50-74</td>
<td>78% at 2 y</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>26-64</td>
<td>67%-96% at 1 y</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>76</td>
<td>72% at 3 y</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>52</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Other therapies summarized in other reviews**
- Calcineurin inhibitor
- High-dose methylprednisolone
- Methotrexate
- Thalidomide
- Hydroxychloroquine
- Clofazimine
- Thoracoabdominal irradiation
- Alefacept
- Infliximab
- Etanercept

Adapted, Flowers & Martin Blood 2015

Mechanistic approach to manage GVHD

Adoptive Treg Therapy
- Purified donor Treg
- Ex vivo expanded Treg
- Antigen-specific Treg

CD4+ Foxp3 Regulatory T cells

Treg-sparing therapy
- sirolimus
- mycophenolate mofetil
- rituximab
- bortezomib

In vivo Treg expansion
- ECP
- low-dose IL-2

B cell depletion in vivo
- rituximab
- datumaximab
- obinutuzumab

Inhibit T cell signaling
- IFN inhibition - brutinib
- JAK1/2 inhibition - ruxolitinib
- PDCO2 inhibition - K/0265
- bortezomib

Inhibit B cell signaling
- BTK inhibition - ibrutinib
- SYK inhibition - fostamatinib
New Drugs for Steroid Failure GVHD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>N patients</th>
<th>Overall Response Rate</th>
<th>FDA approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib (Imbruvica)</td>
<td>Chronic</td>
<td>42</td>
<td>67%</td>
<td>8/2017*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 5 month lasting response</td>
<td></td>
</tr>
<tr>
<td>Ruxolitinib (Jakafi)</td>
<td>Acute</td>
<td>49</td>
<td>57%</td>
<td>5/2019*</td>
</tr>
<tr>
<td>Ruxolitinib (Jakafi)</td>
<td>Chronic</td>
<td>165</td>
<td>50%</td>
<td>Granted priority review</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>compared to 25.6%</td>
<td></td>
</tr>
<tr>
<td>Belomosudil</td>
<td>Chronic</td>
<td>132</td>
<td>75%</td>
<td>Granted priority review</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median duration of response 50 weeks</td>
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GVHD: Challenges

- Wide spectrum of manifestation and severity: diagnosis may be difficult
- No treatment fit all patients
- No idea of who will respond to steroid, concern for under- or overtreatment
- Largely inefficient 1st line treatments, no standard 2nd line measures
- Treatment is toxic, immunosuppressive, might be lifelong
- Impact on quality of life, return to family life, relationships, work
GVHD: New Hope

- We understand this disease better and better
- Improved strategies for prevention
- Lots of work on biomarkers to diagnose and treat correctly and early
- New promising treatments are HERE, more on the horizon
- Improved culture of supportive care, Long Term Follow up, multidisciplinary team

Thank you !!!

My Patients!
My Nurses
My colleagues

BMTInfonet
Pharmacists
Transplant coordinators
Case managers
Social workers
Administrative staff

Visit www.bmtinfonet.org
Questions?

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