**Bone Marrow Failure Syndromes**

Aplastic Anemia and MDS
International Foundation

Thomas Shea, MD
July 16, 2016

---

**Marrow Cells**

Marrow "stem" cells are the cells from which mature blood cells are derived.

- In AA, the marrow is deficient in both stem cells and normal circulating cells leading to decreased RBCs, WBCs, and Platelets.
- In MDS, there are more than usual number of cells, but they can't mature or differentiate into normal RBCs, WBCs, and Platelets the way they should.

Both diseases result in low blood counts, but in one case there are not enough cells, and in the other there are too many marrow cells, but they don't grow up properly.

---

**Normal Peripheral Blood**

Contains RBCs, WBCs, and Platelets

40x magnification

---

**Case**

- 29 yo female artist
- Long term mildly low counts
  - 6/2012: platelets 49, Hgb 7.9, WBC 3.0
- What symptoms might she have?
- Is she a transplant candidate?
- What about heart and lung function and donor availability?
Types of Stem Cell Transplant

<table>
<thead>
<tr>
<th>Type</th>
<th>Source of Stem Cells; Marrow and Blood are often used interchangeably</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous</td>
<td>Patient’s blood or marrow; Stem cell collection f/b 2-4 weeks in the hospital and 2-4 weeks recovery; No GVH</td>
</tr>
<tr>
<td>Used for Lymphoma and Myeloma</td>
<td>Less Toxicity / Higher relapse rate</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>Donor blood or marrow or umbilical cord blood; GVH and graft rejection are possible; 4-5 weeks in the hospital and 2-3 months at the transplant center</td>
</tr>
<tr>
<td>Standard and Reduced-intensity</td>
<td>More toxicity / lower relapse rate</td>
</tr>
<tr>
<td>Used for leukemia, MDS, AA, refractory diseases</td>
<td></td>
</tr>
</tbody>
</table>

Work-up for Stem Cell Transplant

Tests for heart, lung, kidney and liver function for auto and allo pts

Donor Options; the better the match, the better the results
1 in 4 chance for individual sibling match of 8-10 genes
Likely 50% or haplo-identical match for patients with siblings, living parents or living children
Unrelated Donors available for 80% of Caucasians, 50% of AAs and 35% of Asians and Hispanics
Cord blood units are also an option for many pts

Younger age, reliable and available caregivers and fewer comorbidities like diabetes, CAD, lung disease, prior transplant, kidney, or liver disease are better

Treatment: BMT

- Early bone marrow transplantation (BMT) from an HLA identical sibling is indicated as first-line therapy if the patient has severe or very severe disease and is younger than 40 years of age.
- 70–90% chance of long-term cure for those patients younger than 40 years of age.
- Results with donors other than matched siblings are not as good, but are getting better

Case

- 60 yo moves his shop to his garage, but bleeds with tool mishaps.
- Platelets 12k
- DX is MDS, RAEB 2
- Is he a transplant candidate?
Survival after Allogeneic Transplants for Myelodysplastic Syndrome (MDS), 2003-2013

Survival after Allogeneic Transplants for Myelodysplastic Syndrome (MDS), 2003-2013

Survival after Allogeneic Transplants for Myelodysplastic Syndrome (MDS), 2003-2013

Overview

- Major cause of morbidity and mortality after allogeneic SCT.

- Unlike solid organ transplant in which the recipient attacks the donated organ, in GvHD the donor cells attack the recipient.

- Results from a complex interaction between donor and recipient adaptive immunity.

Classifications of GVHD

- Classically divided into acute or chronic based on the time of onset, however symptoms can overlap and occur outside of traditionally recognized time periods

  - **CLASSIC ACUTE GVHD**: present within first 100 days post-hct and display features of acute gvh. Organs involved are usually skin, liver, and GI tract.

  - **CLASSIC CHRONIC GVHD**: may present at any time > 100 days post transplant and can involve skin, joints, eyes, mouth, and GI tract.
Acute Skin GVHD
- Most common, consists of maculopapular rash, usually around the time of WBC engraftment
- Can look like a sunburn and patients may describe as “itchy” or “painful"

Acute Skin GVHD
- Often begins on the nape of the neck, back, chest, palms or soles of feet
- May spread and eventually become confluent

Acute GI GVHD
Pts have diarrhea, N/V and abdominal cramps. Upper and lower endoscopy are key for dx

Treatment of Acute GVHD
- Cornerstone of therapy are topical or systemic steroids
- Maximize tacrolimus levels
- Can add other agents (sirolimus, cellcept, infliximab, ECP) if steroid refractory
- Avoid sun exposure and treat with prophylactic anti-bacterial, anti-viral and anti-fungal prophylaxis

Summary Acute GVHD
- Better matches have best chance of engraftment and less chance of GvHD
- aGVHD occurs after counts have engrafted and during first 1-2 months as an outpatient
- Steroid refractory GvHD is never good
- The more immune suppression we use, the higher the risk of infection
- Advanced, clinical grade III/IV GVHD has a high chance of being fatal

Chronic GVHD
Effector cells in cGVHD
aGVHD: mature T-cells from the donor
cGVHD: immature/maturing T cells from the host

Activated immune cells are not regulated and attack the host tissues leading to tissue damage
Like an autoimmune reaction similar to what is seen with diseases like scleroderma and rheumatoid arthritis
CGVHD Risk Factors

1. Prior acute GVHD
   - HLA disparity between host and donor
     - (HLA matched < HLA matched unrelated < HLA mismatched < HLA mismatched unrelated)
     - Lower incidence in umbilical cord transplant
2. Source of stem cells (PBSCs > BM); More T cells
3. Older age of donor/host
4. Sex mismatching (Parous females > males)
5. DLI infusions can lead to acute or chronic GVHD

CGVHD: Mouth/GI

- Lichen-type features, lacy appearance, restriction of mouth opening from sclerosis
- Esophageal strictures
- Xerostomia
- Pseudomembranes
- Mucosal atrophy
- Anorexia, n/v/d, weight loss
- Failure to thrive

CGVHD: Muscles/ Joints

- Fasciitis, Joint stiffness, Contractures secondary to sclerosis

CGVHD: Eyes

- Dry, gritty, or painful eyes, conjunctivitis, entropion, photophobia, periorbital hyperpigmentation, Elephantis, Corneal irritation

CGVHD: Genital

- Vaginal sclerosis/stenosis
- Lichen planus like features
- Erosions, fissures, or ulcers
- Penile scarring or stenosis
- Painful intercourse

CGVHD: Lung

- Bronchiolitis obliterans organizing pneumonia diagnosed with lung biopsy, PFTs, or CT scans
- Symptoms are usually cough, SOB, fatigue and abnormal breathing tests
CGVHD Treatment

Treatment primarily consists of:

**Steroids**- Systemic and/or Topical
Calcineurin inhibitor therapy- Tacrolimus/ Cyclosporine
Sirolimus
Mycophenolate mofetil (Cellcept)

**Treatments continued**

Monoclonal Antibodies
- Rituximab (Rituxan)
- Entanercept (Enbrel)
- Anti-Thymocyte Globulin (ATG)
- Imatinib or Dasatanib
- Alemtuzumab (Campath)

ECP or Extra Corporeal Photophoresis

Topical therapies for eyes. Inhaled steroids for lungs, wound and meticulous skin care

Graft Vs Tumor Effect

- Not all GvHD is bad!
- Can be manipulated as a form of immunotherapy
- In some disease states, donor T-cells that are attacking the host body are also finding and eliminating malignant residual host T-cells
- In some studies, this has shown to decrease the risk of relapse and **improve overall survival**
- Best observed in CML, some AML and MDS

- **Do we need or want this in AA? NO!!!!!!**

Transplants for AA and MDS

Caregiver and Survivorship Issues

Impossible to underestimate….

- The immediate often overwhelming impact on patients’ and caregiver’s lives
- The importance of supportive caregivers

Immediate impact….

- Initial transplant usually requires hospitalization of 2-6 weeks which impacts:
  - Job duties
  - Family duties and childcare
  - Financial obligations
  - This is in addition to time required for initial treatment prior to transplant
- Transplants for MDS and AA are nearly always allogeneic transplants
- **Costs of medications and out of pocket expense for housing, transportation and living expenses can be HUGE**
When Stem Cell Transplant Required

- Dedicated caregiver identified
  - Trained by transplant nurses, doctors
  - Must have transportation
  - Family, friends, etc.
  - FMLA is a must for those who must miss work.
- Allogeneic transplants require a caregiver at patient’s side for first 100 days
- Autologous transplants are usually much less intensive and of shorter duration
  - 2-3 weeks in hospital and 2 weeks in clinic

Duration of disability

- Depends on type of job
  - Very hard to continue physical work
  - Some employers may be flexible with “work from home” type jobs
- For allogeneic transplant—generally 12 months after transplant
- For autologous transplant—generally 3-6 months after transplant
- This is in addition to time for induction and pre-transplant therapy

Keys to surviving job / $$ stresses

- Immediate applications for at least short term disability
- For transplant—consider long term disability / SSD
- Use social worker to help
- For transplant—maintain insurance coverage / obtain Medicaid
- Open conversation with employer

Survivorship

- Begins at diagnosis
- More of a focus at the conclusion of treatment
  - How to get back to work
  - How to get back to family obligations (as if they ever went away)
- Ongoing physician visits
  - Many programs are focusing increasingly on survivorship

Late effects of MDS or AA Transplant

- Mental health—trauma of receiving the diagnosis
- Fertility—discuss prior to starting treatment
  - Reproductive endocrinology consultation
- Cognitive function:
  - “chemo brain”
  - Brain irradiation for some leukemias
- Increased risk of other cancers

Exercise Resources

- BMT Infonet (bmtinfonet.org)
- http://members.acsm.org
  - Find a certified cancer trainer in your area
- Livestrong.org
  - Find a YMCA LiveStrong program in your area
- Your physician may have access to local resources that fit your needs
Ask for help….

- UNC CCSP
  - Mental health services
  - Resource center
  - Pastoral Care
  - Supportive care
  - Survivorship program
- LLS
  - Peer-to-peer program
  - Family support groups
  - Financial aid programs
  - Online chats
  - Back to school program

Location of Centers Participating in the CIBMTR 2015

Annual Number of Transplant Recipients in the US by Transplant Type

Allogeneic Transplant Recipients in the US, by Donor Type

Unrelated Donor Allogeneic Transplants in Patients Age >20 years

Indications for Hematopoietic Stem Cell Transplants in the US, 2013
Allogeneic Transplants Registered with the CIBMTR

by Conditioning Regimen Intensity

Reduced Intensity  Myeloablative