Bone Marrow Failure Syndromes

Aplastic Anemia and MDS International Foundation

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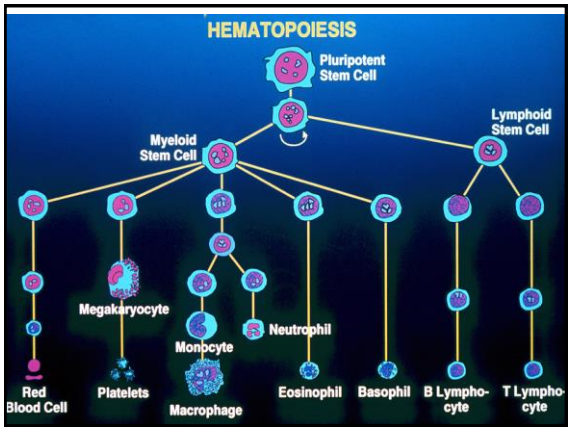
Marrow Cells

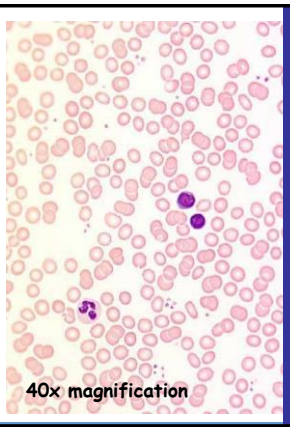
Marrow "stem" cells are the cells from which mature blood cells are derived

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

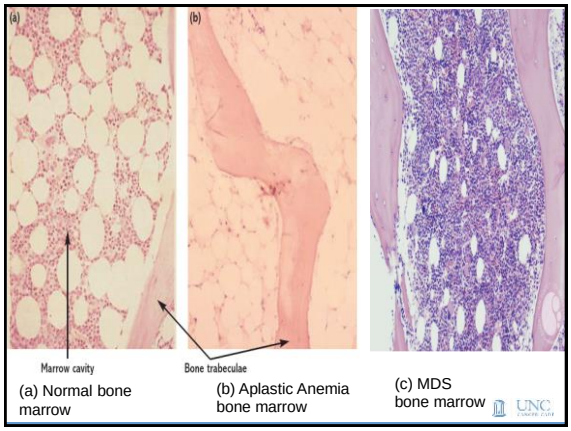
Both diseases result in low blood counts, but in one case there are not enough cells and in the other there are too many marrow cells, but they don't grow up properly





Normal Peripheral Blood

- Contains RBCs, WBC,s and Platelets



Case

- 29 yo female artist
- Long term mildly low counts
  - 9/2011: WBC 3.3, plt 108, Hgb 12
  - 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

Types of Stem Cell Transplant

Type	Source of Stem Cells; Marrow and Blood are often used interchangeably
Autologous used for Lymphoma and Myeloma	Patient's blood or marrow Stem cell collection f/b2-4 weeks in the hospital and 2-4 weeks recovery; No GVH Less Toxicity / Higher relapse rate
Allogeneic Standard and Reduced-intensity Used for leukemia, MDS, AA, refractory diseases	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 More toxicity / lower relapse rate

Work-up for Stem Cell Transplant

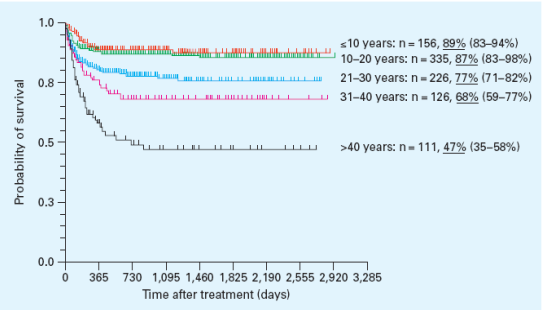
Tests for heart, lung, kidney and liver function for auto and allo pts

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 co-morbidities like diabetes, CAD, lung disease, prior transplant, kidney, or liver disease are better

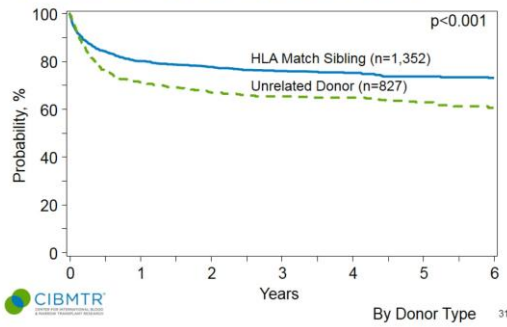
Treatment: BMT

- 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



Actuarial survival for patients undergoing HLA identical sibling bone marrow transplantation for severe aplastic anaemia according to age.

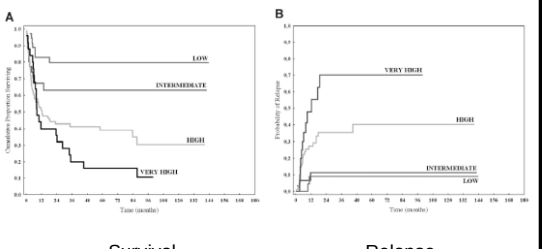
Survival after Allogeneic Transplants for Severe Aplastic Anemia, ≥20 Years, 2003-2013



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?

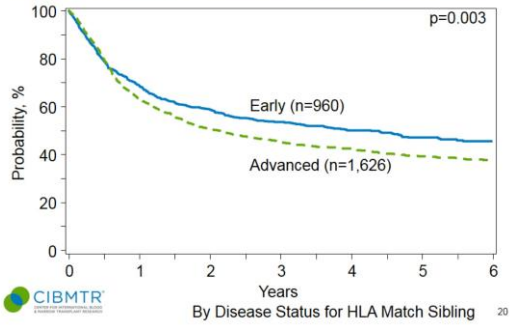
SCT Outcomes by WPSS



Survival Relapse

Paolo F, et al. Blood 2008; 112: 895-902

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



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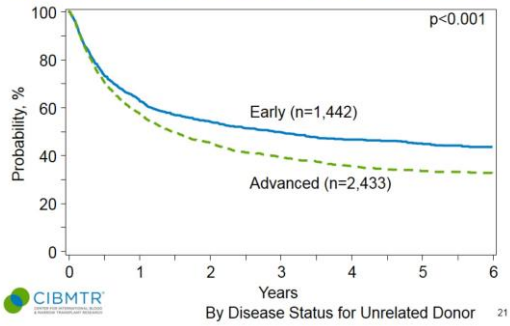
By Disease Status for HLA Match Sibling 20

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



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By Disease Status for Unrelated Donor 21

Acute and Chronic Graft Versus Host Disease or GVHD

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Overview

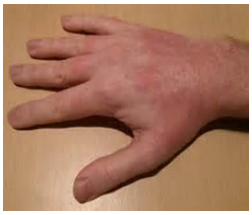
- Major cause of morbidity and mortality after allogeneic SCT.
- Unlike solid organ transplant in which the recipient attacks the donated organ, in GvHD the donor cells attack the recipient.
- Results from a complex interaction between donor and recipient adaptive immunity.

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 gvhd. 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

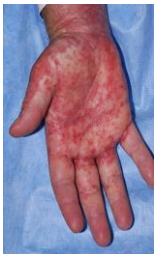
Acute Skin GVHD

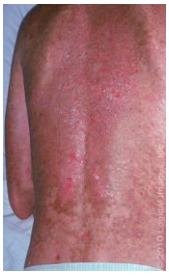
- Most common, consists of maculopapular rash, usually around the time of WBC engraftment
- Can look like a sunburn and patients may describe as “itchy” or “painful”



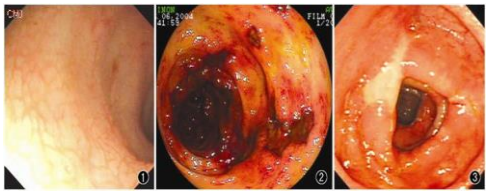
Acute Skin GVHD

- 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

Treatments include steroids, ECP, IV alimentation and other agents as needed

These pts are usually hospitalized and are sick!

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
   1. 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 a
  opening from sclerosis
- Esophageal strictures
- Xerostomia
- Pseudomembranes
- Mucosal atrophy
- Anorexia, n/v/d, weight loss,
- Failure to thrive

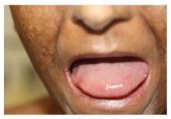
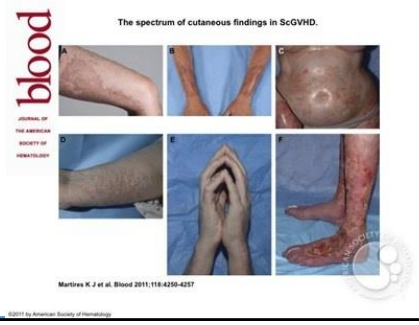


Figure 4 – Lip atrophy and restriction of mouth opening from sclerosis

CGVHD: Muscles/ Joints

- 

CGVHD: Eyes

- Dry, gritty, or painful eyes, conjunctivitis, entropion, photophobia, periorbital hyperpigmentation, Blepharitis, Corneal irritatio

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

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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 consulation
- 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

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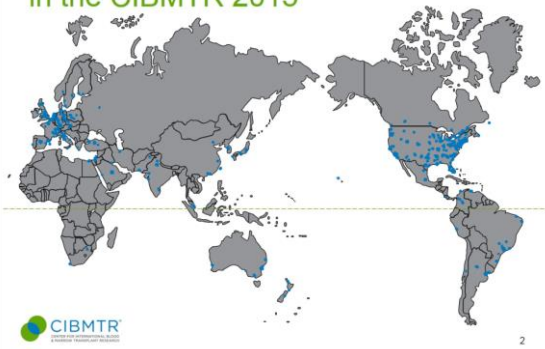
Location of Centers Participating in the CIBMTR 2015



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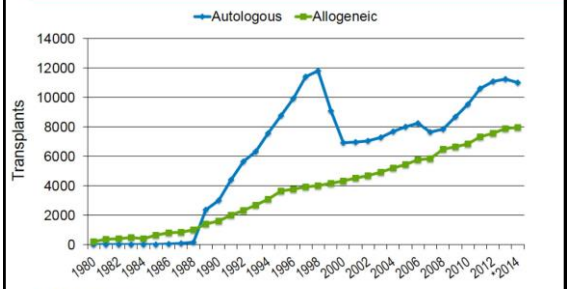
Annual Number of Transplant Recipients in the US by Transplant Type



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*2014 Data incomplete

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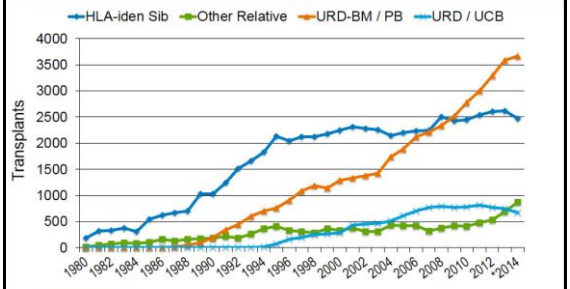
Allogeneic Transplant Recipients in the US, by Donor Type



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*2014 Data incomplete

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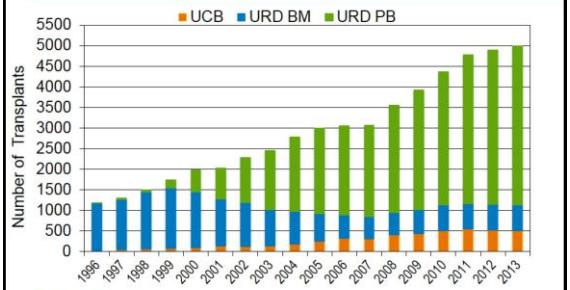
Unrelated Donor Allogeneic Transplants in Patients Age >20 years



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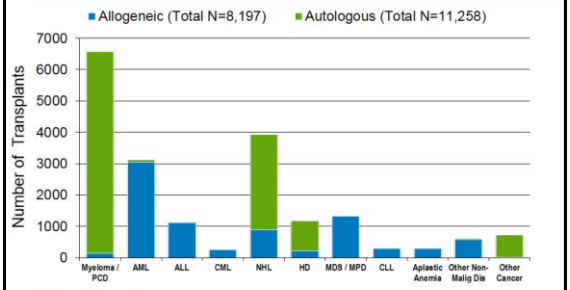
Indications for Hematopoietic Stem Cell Transplants in the US, 2013



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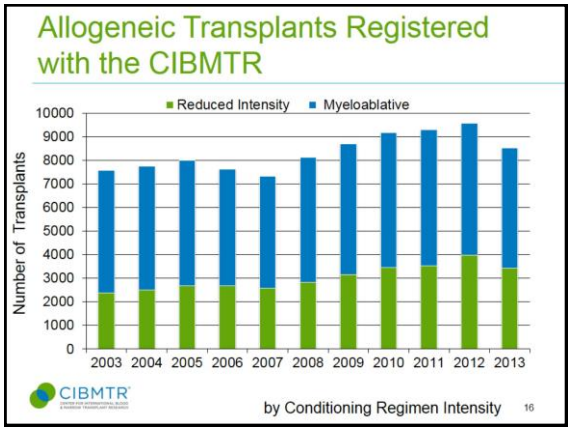
Allogeneic Transplants Registered with the CIBMTR
Reduced Intensity
Myeloablative
Number of Transplants
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013
CIBMTR
by Conditioning Regimen Intensity
16