Aplastic Anemia & MDS INTERNATIONAL FOUNDATION

Understanding BMT: Before, During, and After Transplant

(BMT 101)

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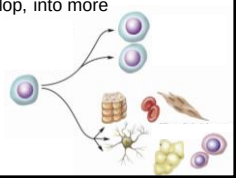
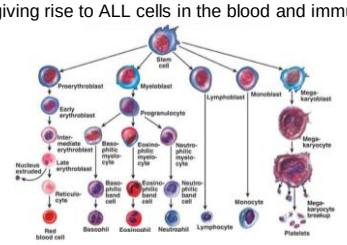
Definitions

- Stem Cell Transplantation (aka BMT)
  - The transfer of Hematopoietic Stem Cells from Donor to Recipient
- What is a Stem Cell?
  - Stem cells are defined by two characteristics:
    - They can make copies of themselves, or *self-renew*
    - They can *differentiate*, or develop, into more specialized cells



Definitions

- Are there different types of Stem Cells?
  - Embryonic / Pluripotent Stem Cells
  - Tissue Specific Stem Cells
    - Hematopoietic Stem Cells – A stem cell capable of giving rise to ALL cells in the blood and immune system



Rationale for Transplantation

- Elimination AND Replacement of:
  - Diseased marrow
  - Poorly functioning marrow
  - Immune compromised marrow
  - Metabolically compromised marrow
- Protection against ultra-high doses of chemoradiotherapy
- Establish immunologic platform for immunotherapy

Types of Transplantation

Autologous

- High doses of chemotherapy and/or radiation
- Designed to kill tumor; overcome resistance with dose intensity
- Requires stem cell rescue
- *Not really a transplant*

Allogeneic

- 2 mechanisms to cure:
  - Immunologic: Donor vs. Host (Graft vs. Tumor)
  - Chemotherapy and/or radiation

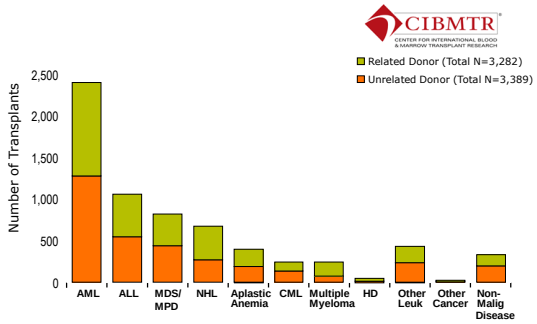
Decision to use autologous/allogeneic marrow source is disease, stage and patient specific

Indications for Transplantation

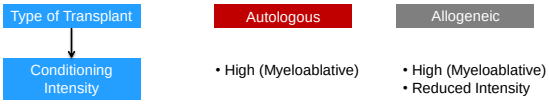
- Autologous
  - Multiple Myeloma in remission
    - Prolongation of remission
  - Diffuse Large B Cell NHL in 2nd remission
  - Hodgkin Disease in remission
  - Mantle Cell NHL
  - Some Germ Cell Tumors
  - AML, in very rare circumstances

Curative Intent

Indications for Transplantation - Allogeneic



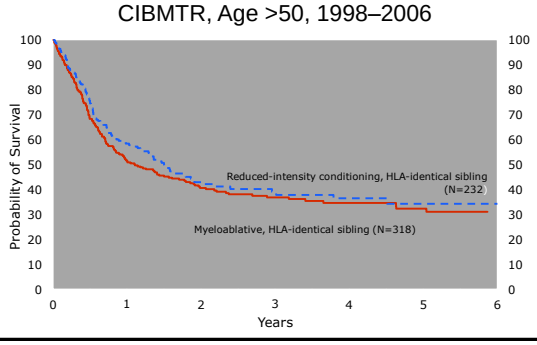
Stem Cell Transplant Decision Tree



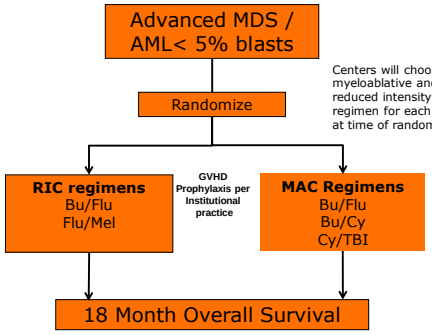
Conditioning Regimen

- Determined by:
  - Primary tumor type
  - Stage of disease at transplantation
  - Graft vs. tumor effect in that disease
  - Performance status/comorbidity of recipient
- Large variety of regimens exist
- Differ in intensity and toxicity
  - Ablative is Hard; RIC is pretty easy
- We have "Recipes" for these regimens

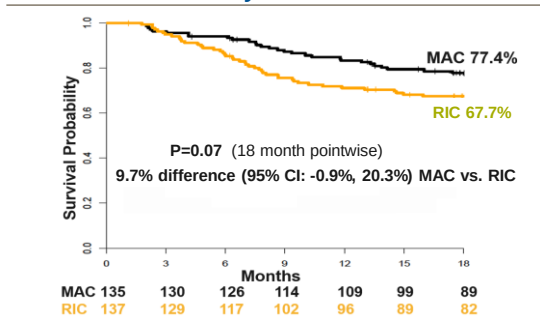
What is Better? Myeloablative or RIC?



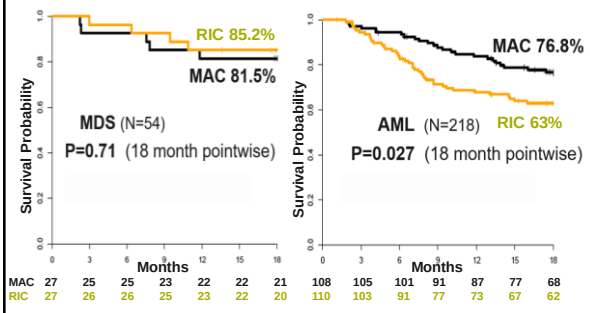
BMT CTN 0901



Overall Survival by Treatment Arm



Overall Survival by Disease Group



MAC	27	25	25	23	22	22	21	108	105	101	91	87	77	68
RIC	27	26	26	25	23	22	20	110	103	91	77	73	67	62

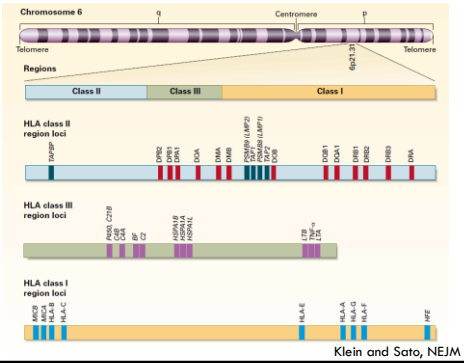
Stem Cell Transplant Decision Tree

Type of Transplant	Autologous	Allogeneic
Conditioning Intensity	• High (Myeloablative)	• High (Myeloablative) • Reduced Intensity
Donor Type	• Self	• Related • Unrelated
Degree of Match	• Perfect	• Matched • Mismatched • Highly Mismatched

Finding a Donor

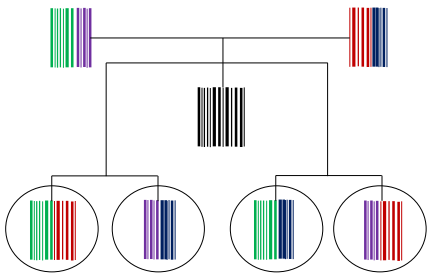
- Goal is to MATCH donor-recipient pairs
  - Not a problem in Autologous transplantation
  - Identical Twins (Syngeneic Transplantation) not commonly found nor used
- Matching performed for HLA (Human Leukocyte Antigen) molecules, encoded by MHC complex (Major Histocompatibility Complex)
- Matching at non-HLA loci also important, but not done (yet).

The HLA System

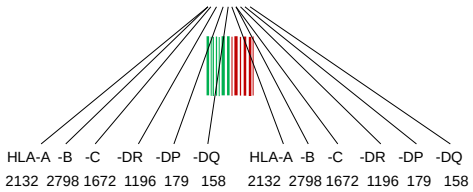


Klein and Sato, NEJM 2000

Histocompatibility

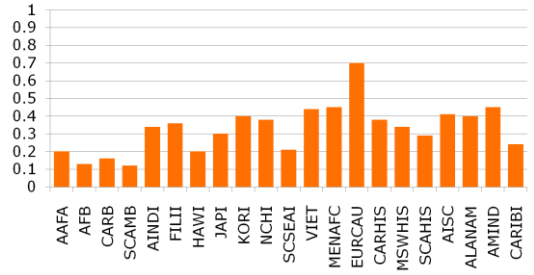


Histocompatibility – Unrelated Donors



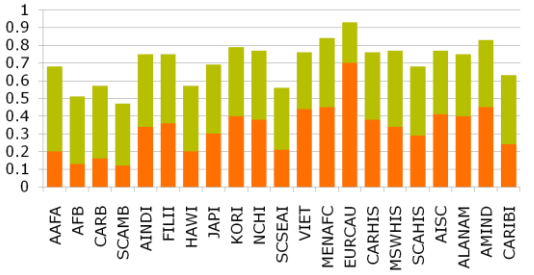
Nearly Infinite Possible Combinations!!!

"Perfect" Match Rates in the Adult Donor Registry



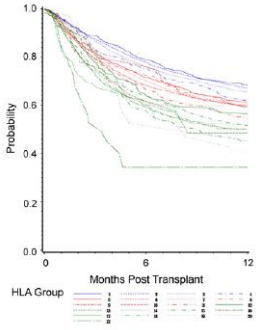
Courtesy Martin Maiers, NMDP Bioinformatics

"Perfect" and "Pretty Good" Match Rates in the Adult Donor Registry



Courtesy Martin Maiers, NMDP Bioinformatics

Does the Degree of Match Matter?



Weisdorf, BBMT 2008

Stem Cell Transplant Decision Tree

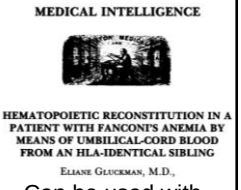
Type of Transplant	Autologous	Allogeneic
Conditioning Intensity	• High (Myeloablative)	• High (Myeloablative) • Reduced Intensity
Donor Type	• Self	• Related • Unrelated
Degree of Match	• Perfect	• Matched • Mismatched • Highly Mismatched
Stem Cell Source	• Bone Marrow • PBSC	• Bone Marrow • PBSC • Umbilical Cord Blood

Stem Cell Source

	Bone Marrow	Peripheral Blood Stem Cells	Umbilical Cord Blood
Ease of Collection			
Engraftment			
Immune Reconstitution			
GVHD Rates			
Graft-vs.Tumor			

Umbilical Cord Blood – A New Alternative

- Medical waste – Procured at the time of delivery
- Contains hematopoietic stem cells – Can be used for transplantation

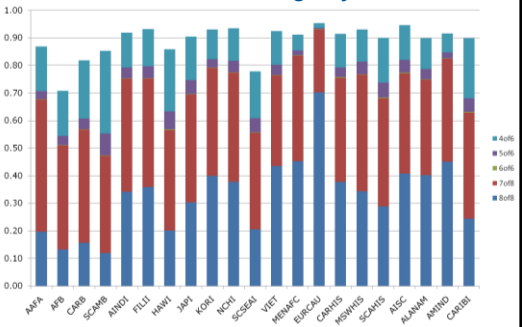

MEDICAL INTELLIGENCE

HEMATOPOIETIC RECONSTITUTION IN A PATIENT WITH FANCONI'S ANEMIA BY MEANS OF UMBILICAL-CORD BLOOD FROM AN HLA-IDENTICAL SIBLING

ELIANE GLUCKMAN, M.D.,

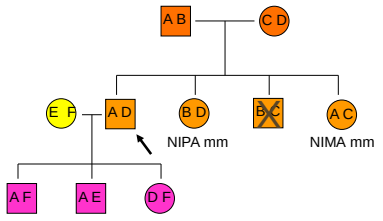
- Immunologically "immature" – Can be used with less stringent matching

“Perfect”, “Pretty Good” and UCB Match Rates in the Adult Donor Registry



Courtesy Martin Maiers, NMDP Bioinformatics

Haploidentical Transplantation



Preparing for Transplantation

- Pre-Transplant Testing
  - Blood tests: Kidney, Liver function, Infectious disease
  - Functional tests: Heart, Lung
  - Psychosocial interviews
  - Financials
- Pre-Transplant Teaching
  - Restrictions / Safety
  - Nutrition
  - Medication

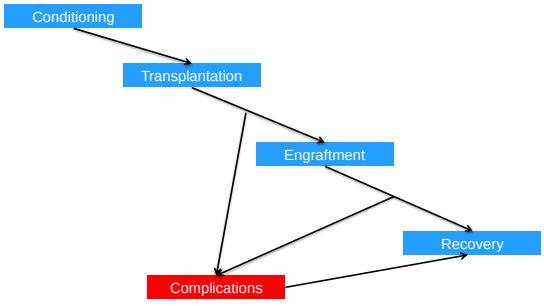
Preparing for Transplantation

- Consent Session
  - Should be VERY thorough
  - At least an hour
  - Ask a lot of questions
  - Be prepared to be offered participation in Research studies

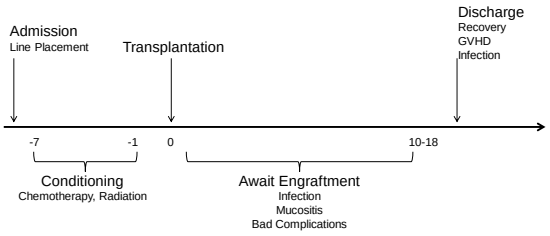
Other Things To Do Pre-Transplant

- Go see a bunch of movies
- Go out to eat
- Gain some weight
- Have a party

Grand Overview of Transplantation



Transplantation Timeline



Post-Transplantation

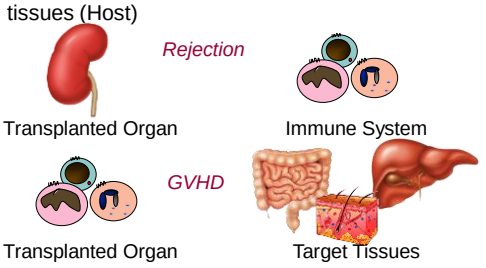
- A lot of 'alone' time
  - Designed to PROTECT you
- Frequent visits to the clinic (big social outing of the week)
- Lots of medications
- Complication time
- You won't feel great. Yet.

GVHD - Background

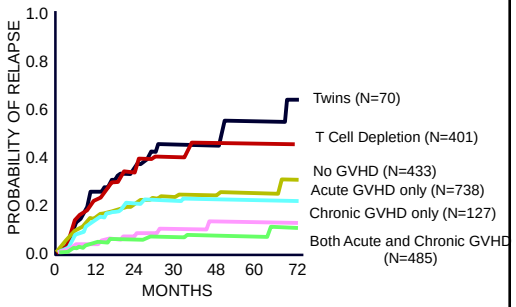
- After disease relapse, GVHD is the most common cause of treatment failure after transplantation.
- 2 syndromes:
  - Acute GVHD
  - Chronic GVHD
    - Previously defined by temporal relationship to time of transplantation
    - Now defined by clinical features
    - Differences in pathobiology

GVHD

- Caused by the interaction between the transplanted immune system (Graft) and recipient tissues (Host)

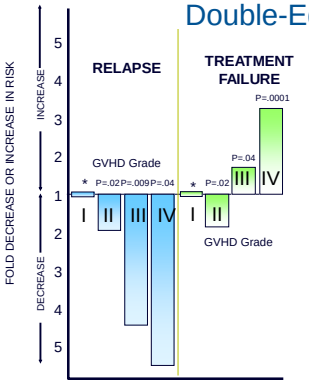


Graft-vs.-Leukemia



Horowitz *et al*, Blood 1990

Double-Edged Sword



Horowitz *et al*, Blood 1990

Acute GVHD

Incidence:

- 35% after Related Donor Transplantation
- 50% after Unrelated Donor Transplantation

Despite prophylaxis

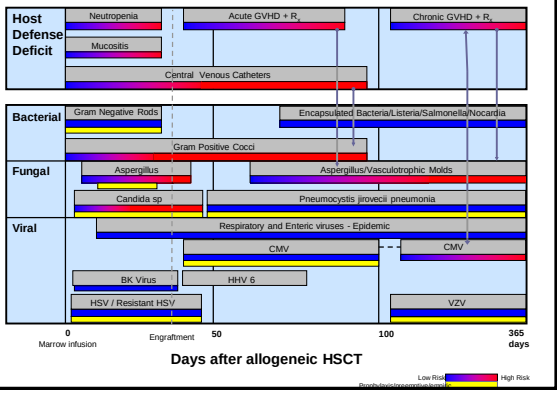
- Current Standard: Tacrolimus/Cyclosporine and Methotrexate

Factor	Condition That ↑ Risk of Acute GVHD
Donor-Recipient Factors	
Major HLA Disparity (HLA Class I, II)	HLA Mismatched donor > Matched Donor
Minor HLA Disparity (mHA)	Unrelated Donor > Related Donor
Sex Matching	Mismatch > Match
Donor Parity	Multiparity > Nulliparity
Donor Age	Older donor > Younger Donor
ABO type	ABO Mismatch > ABO Match
Donor CMV Serostatus	CMV positive > CMV Negative
Cytokine Gene Polymorphisms	Numerous Associated with Acute GVHD
Stem Cell Graft Factors	
Stem Cell Source	PBSC > BM > UCB
Graft composition	Higher CD34+ count > Lower CD34+ cell count*
	Higher T cell dose > Lower T cell dose*
Transplantation Factors	
Conditioning Intensity	Myeloablative > Reduced-intensity Regimens

Acute GVHD

- Clinicopathologic syndrome
  - Skin
    Erythematous rash → Bullae → Desquamation
  - Liver
    Hyperbilirubinemia → Hepatic failure
  - Gut
    Secretory diarrhea → Ileus

Infection



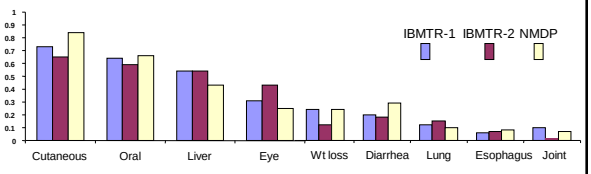
Post-Transplantation – Beyond 100 Days

- 2 Main issues
  - Middle Term Complications
  - Late Effects and Survivorship

Chronic GVHD - Background

- >50% of Related and Unrelated Recipients
  - Incidence increasing as early transplant outcomes improve
- Important cause of morbidity in the later post-transplant period
  - Most have more than 1 organ system involved
- Median 2-3 years of treatment
- Associated with Quality of Life and functional deficits

Chronic GVHD – Organ Involvement



Adapted from Lee *et al*, 2002

SYSTEM	SIGNS	SYMPTOMS
SKIN AND RELATED STRUCTURES	**Skin**: Hyper/hypopigmentation, lichenoid, sclerodermal, papulosquamous, ichthyosiform and psoriasiform changes. Atrophy, poikiloderma and ulcers. **Nails**: dystrophy, longitudinal ridging, onycholysis, pterygium, destruction. **Scalp**: scaling, fibrosis, scarring and non-scarring alopecia, papulosquamous changes.	Pruritus, dryness, pain, infection, rigidity, decreased range of motion, photosensitivity. Nail and hair loss.
MOUTH	Lichenoid changes, erythema, ulcers, xerostomia, fibrosis, leukoplakia. Dental caries.	Pain, odinophagia, dysphagia, dysgeusia, dryness, sensitivity to food.
EYES	Keratoconjunctivis sicca, corneal ulcerations.	Pain, dryness photophobia.
MUSCULOSKELETAL	Polymyositis, muscle weakness, myalgias, arthritis, arthralgias, fasciitis.	Weakness, arthralgias, myalgias, decrease ROM
GI TRACT	**Upper**: Abnormal motility, esophageal fibrosis, ulcerations, strictures. **Lower**: Mucosal abnormalities/malabsorption, submucosal fibrosis	Odynophagia and lower dysphagia, pain, heartburn, nausea, anorexia, vomiting, abdominal pain, diarrhea/malabsorption, dehydration, weight loss

SYSTEM	SIGNS	SYMPTOMS
LIVER	Hyperbilirrubinemia, elevated Alk P, elevated ALT/AST, fibrosis.	Fatigue, jaundice, pruritus.
LUNG	Obstructive (BO/BOOP) or restrictive (scleroderma of the chest) dysfunction. Air trapping, bronchiectasis, pneumothorax, pneumomediastinum, subcutaneous emphysema. Microbial colonization or pneumonia.	Dyspnea, wheezing, productive or non productive cough.
NEUROLOGIC	Neuropathy, myasthenic syndromes.	Pain, burning, dysesthesias, paresthesias, muscle weakness
VAGINAL MUCOSA	Erythema, lichenoid changes, dryness, ulcers, strictures/stenosis.	Pain, burning, dryness, Dyspareunia
SEROSAL	Serositis, pericardial, pleural and peritoneal effusions.	Dyspnea, chest pain, pleuritic pain, abdominal pain, ascites.
HEMATOPOIETIC	Isolated or combined cytopenias, eosinophilia, hemolysis.	Fatigue, fever, infection, bleeding.
IMMUNOLOGIC	Repeated infections of various etiologies, lymphopenia, Hyper/hypogammaglobulinemia	Increased susceptibility to infection.

Treatment Strategy

- Local Symptoms → Local Rx
  - Early identification crucial
  - Supportive vs. Local immunosuppressive
  - **National Institutes of Health Consensus Development Project on Criteria for Clinical Trials inChronic Graft-versus-Host Disease: The 2014 Ancillary Therapy and Supportive Care Working Group Report.**
    Biology of Blood and Marrow Transplantation, 2015
    - Can be accessed through ASBMT Website:
      http://www.asbmt.org/?page=GuidelineStatements

Treatment Strategy

- Systemic Symptoms / Multiple Local Sites → Systemic Rx
- Initial Rx:
  - Prednisone 1 mg/kg/day
  - Tacrolimus: 5-10 ng/ml *or*
  - Cyclosporine: 200-400 µg/L
- Complete Response Rate: 50-55%
- Median Time to Discontinue Immune Therapy:
  1.6 – 2.2 years!!
- Multiple Clinical Trials available – You should participate!!!
  - www.clinicaltrials.gov

Post-Transplant Transitions

- You will experience a number of transitions post transplant
  - Gaining more independence and freedom - welcomed yet *very* stressful
  - Relationships with family/friends/loved ones-going through a time of adjustment
  - Financial pressures – Going/not going back to work
- Acknowledge the enormity of your experience
  - The reality of your diagnosis
  - The trauma inherent in transplant
  - The loss of who you were and the security you previously felt
  - Seek help if you are stuck

Psychosocial Effects of BMT

- BMT survivors generally experience a high global quality of life
- Some problems may be persistent
  - Low energy, sleep problems
- Emotional or psychological distress can be common

- Depression
  - Frequently observed
  - Exact prevalence rates unknown
  - Depression before and after transplant can affect morbidity and mortality
  - Treatment is important

  - Women more likely to have current depression (75% v 25%, p=.007)
  - Women more likely to receive antidepressants (92% v 50%, p=.02)
  - People with treated depression are similar to those without depression

DeMarinis et al., European J of Cancer Care

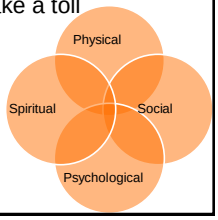
Changing Emotions

- Recovery is a slow process

- Emotions some experience after transplant:
  - Frustration: Lack of energy to do what you once did
  - Anger: Why do I have GVHD? Why can't I just feel normal?
  - Guilt: Being a burden to caregiver/family/loved ones
  - Mood Changes: "up and down"--caused by medications (steroids)
  - Depression/Anxiety

Quality of Life

- Fatigue: Patients give up being as they were
- Work: full-time, part-time, permanent disability
- Recreation: This can change too. Figure out what you CAN do.
- Relationships: Transplant can take a toll
- Chronic Graft vs. Host Disease



Cognitive Changes

- Clinical evaluation for neurologic dysfunction is warranted
  - Neuropsychological testing
  - Additional tests may be indicated
- What we know
  - Pre HSCT deficits are common
  - Post HSCT deficits are even more common
- Complication rates
  - Allogeneic (Unrelated > Related) >> Autologous
- Types of complications
  - Late CNS infections
  - Cerebrovascular complications
  - 20% will report impaired memory, attention span, verbal fluency

Sexuality after Transplant

- Important QoL issue
- Sexual dysfunction is a common, enduring consequence of systemic cancer treatment
- Changes in body image, decline in perceived attractiveness
- Infertility for both men and women
- Majority of survivors say they were not prepared for changes in sex life
  - Women: Ovarian failure → low estrogen levels and vaginal GVHD → stenosis, mucosal changes → pain, irritation and sensitivity
  - By 2 yrs, there is improvement compared to 6 months, but quantity and quality still not what it was even 5 yrs later

  - Men: Gonadal and cavernosal insufficiency → ED and lower libido
  - Rates of sexual activity improve by 1 year, but takes 2 years to see improvement in quality and quantity. At 5 years still lower function compared to no BMT group

Coping Strategies

- Recognize the impact has been physical, emotional, psychological and spiritual
- Go at your OWN pace, not an 'expected' pace
- Your situation, coping style may be different from others - that's OK!
- Be open, be honest about your feelings and needs
- Try to process what you are experiencing with a loved one or a professional
- Ask what would be most helpful to me now?
  - Support group
  - One on one counseling
  - Reading

Taking care of yourself

- Take your medications
- Make your appointments
- Respect your altered immune function
- Mind your emotional well being
- Get enough sleep
- Pay attention, keep lists, make associations
- Consider cognitive rehabilitation services
- Keep your perspective
  - Do not over-generalize
  - Time heals all?
- Nutrition
- Exercise

Dietary Challenges after Transplant

- Weight gain or loss
- Appetite changes
  - Small, frequent meals
  - Avoid eating snacks too close to meal times
  - Choose nutrient dense foods
  - Fortify foods to boost calories
  - Try new recipes
- Lack of interest in food
- Taste alterations / Dry Mouth
  - Drink plenty of fluids, at least 8 cups per day
  - Moisten foods with gravies, sauces, or broth
  - Limit caffeine
  - Artificial saliva products
- Steroids, GVHD

Post-Transplant Diet

- Eat 5-10 servings fruits & veggies each day
  - 1 serving = 1/2 cup cut, cooked or sliced; 1 piece medium fruit; 1 cup leafy greens
- Re-shape your plate
  - 1/2 veggies, 1/4 protein, 1/4 whole grains
- Emphasis on variety
- Look for richly colored plant foods
- Emphasize whole grains
  - Reduce risk for certain cancers, diabetes and heart disease
  - Keep weight off
  - Lower cholesterol levels
  - Promote digestive health
- Reduce consumption of saturated and trans- fats, increase monounsaturated and omega-3 Fats

Focus on Physical Activity

Physical Activity + Proper Diet = Healthy Weight

- **Create an individualized fitness plan**
  - Always talk with your doctor first
  - Schedule time for activity each day, remember every bit counts
  - Ensure intensity appropriate
  - Choose activities you enjoy
  - Find a workout “buddy”
- **Incorporate key components**
  - Cardiovascular exercise, strength, flexibility and relaxation

Returning to Work

- Up to 89% of BMT patients return to work or school within 5 years after treatment.
- Influences that impact the ability to return to work are:
  - Age
  - Gender
  - Education
  - Personal values
  - Perceived advantages of work
- Influences that impact the INability to return to work:
  - Physical demands
  - Job Lock
  - Employer accommodation
  - Fear of disclosure
  - Perceived discrimination
- Data suggests BONE MARROW recipients more likely to return to work than PBSC recipients (Lee, ASH 2015)

Employer Accommodation

Accommodation: Aiding an employee to perform their job by providing modifications.

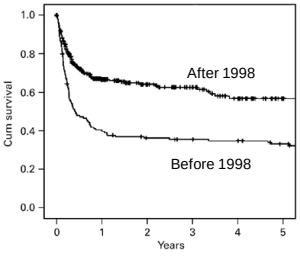
“Reasonable” accommodations

- Change in duties
- Change in work hours
- Flexible work hours
- Periodic rest breaks
- Allow employees to work from home
- Modify dress code

Caregivers

- Acknowledge the long haul of BMT caregiving
  - Physical demands
  - Feelings of loss, anger, fatigue, resentment, hope
- Change has been difficult, you have HAD to adapt to the change-shift in roles
- Sometimes paddling in the same direction as your loved one is difficult
- Every relationship/family functions differently
- As a caregiver, must adapt to what works best for you
- Make time for yourself
- Rely upon others (transportation, child care, meals)
- Say NO to non-essential needs – Prioritize!

Survivorship in BMT



- Donor-recipient matching
- GVHD prophylaxis anfd treatment
- Supportive care

Survivorship in BMT

- 2 components:
  - Surviving Malignancy
  - Surviving Transplantation
- Different sets of risks and complications need to be considered

Medical Monitoring after BMT

Majhail *et al*. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation.
Biology of Blood and Marrow Transplantation, 2012

Antin JH. Long term care after hematopoietic –cell transplantation in adults.
New England Journal of Medicine, 2002

Medical Monitoring

Organ	Risk	Outcome	What To Do?
Mouth	Radiation, cGVHD	Dryness, Caries	Regular dental exams Monitor for oral cancers

Medical Monitoring

Outcome	Risk	What To Do?
Infection	cGVHD, Immune Suppression	Prophylaxis

Allogeneic BMT Survivorship Clinic

- Target population
  - Allogeneic recipients of high-dose myeloablative conditioning
  - Alive, without malignancy, 12 months after transplantation
  - May have evidence of chronic GVHD
  - Total treatment considered
    - Chemotherapy to treat malignancy
    - Focal radiotherapy to treat malignancy
    - High-dose chemotherapy for transplant prep
    - Total body irradiation for transplant prep

Allogeneic BMT Survivorship Clinic

- Multidisciplinary clinic
  - 1x/month, capture all patients (voluntary) for a one time consultative visit
- Goals of the clinic
  - Develop wellness plan to address the needs of this high risk group
  - Develop an individualized follow up plan to address the non-GVHD related risks of transplant survivors

Allogeneic BMT Survivorship Clinic

- Providers
  - BMT Specialists: MD and NP – Endocrine, cardiovascular, respiratory, bone, sexuality, cancer screening
  - Dermatology
  - Oral Medicine
  - Ophthalmology
  - Exercise Physiology
  - Nutrition
  - Psychosocial Counselor
- Patients will be followed annually by NP for their survivorship needs, outlined in the wellness plan
- Research Agenda

Treatment summary

- Diagnostic tests performed and results
- Tumor characteristics (e.g. site, stage, grade, markers)
- Dates of treatment initiation and completion
  - Surgery, radiotherapy, chemotherapy, including agents used
- Treatment regimen, total dosage, clinical trials (if any), and toxicities experienced during treatment
- Psychosocial, nutritional, and other supportive services
- Contact information on treating institutions and providers
  - Identification of a key coordinator of continuing care

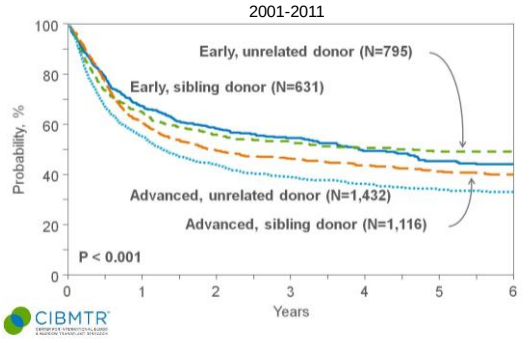
More Resources in BMT

- National Marrow Donor Program
  - www.bethematch.org
  - Smartphone app (excellent)
- BMT InfoNet
  - www.bmtinfonet.org
- nbmtLink
  - www.nbmtlink.org

- Questions?

Transplant for MDS and AA

HSCT Outcomes - MDS



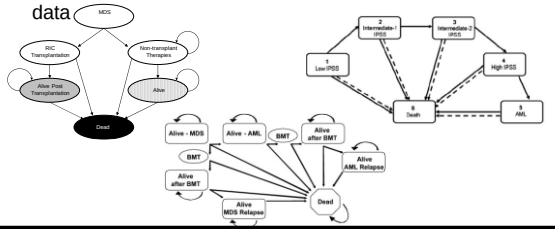
Timing of HCT for MDS

When?

Not too early, but not too late

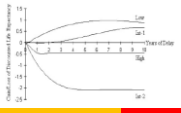
Probably no single formula to fit all patients

Markov Models useful since there is NO randomized data



Summary of Decision Models

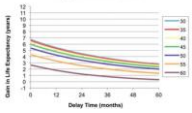
Myeloablative, Sibling Donor Cutler 2004

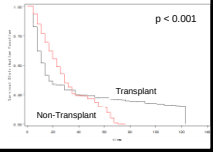


Low Risk IPSS	Int-1 Risk IPSS	Int-2 Risk IPSS	High Risk IPSS

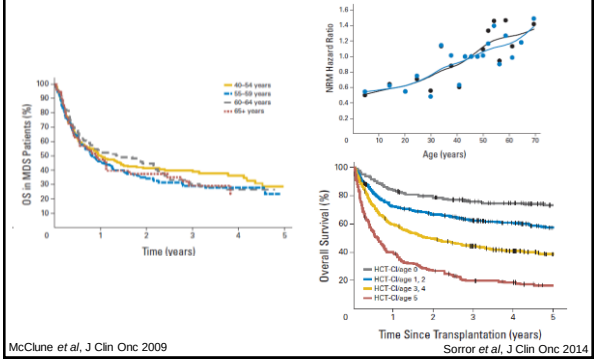
RIC, Sibling or Matched, Unrelated Donor Koreth 2013

RIC or Ablative, Sibling or Matched, Unrelated Donor Allesandi





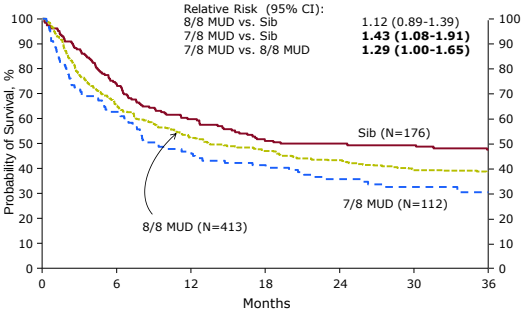
Age and Comorbidity



McClune *et al*, J Clin Onc 2009

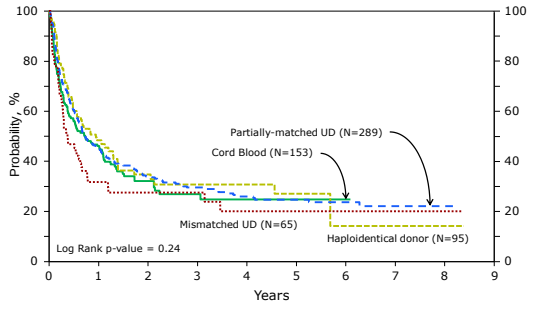
Sorror *et al*, J Clin Onc 2014

Donor Availability



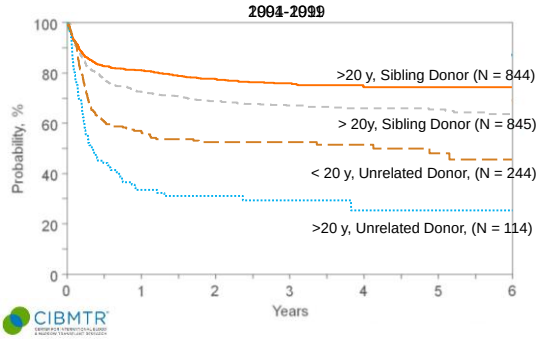
Saber *et al*, Blood 2013

Donor Availability



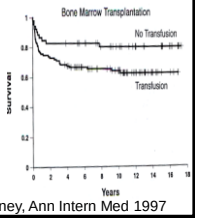
Courtesy W. Saber

HSCT Outcomes - SAA



HCT for SAA

- This is an HCT EMERGENCY
- HLA type IMMEDIATELY
  - Serologic family typing available often in 1-2 business days
- Avoid Transfusion if possible
  - Permissive anemia
  - Permissive thrombocytopenia



Doney, Ann Intern Med 1997