Bone Marrow Transplantation for Severe Aplastic Anemia

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Conference Objectives (cut and pasted from AAMDS.ORG)

- Learn how to stand up for your health, take charge of your care and become a more powerful patient.
- Learn more about your diseases, current treatments and emerging therapies.
- Get your questions answered. Plenty of time will be provided in every session.

Objectives for This Talk

- Basic Concepts of Bone Marrow Transplantation
  - Teach you the language of BMT
  - Describe the process of BMT
  - Empower you to ask the right questions
- Review of Recent Data for outcomes for children and adults
  - Short term and long term data
- Answer Questions (if possible, avoiding personal questions)

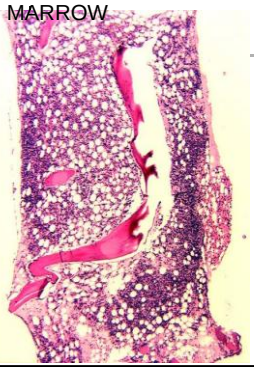
Glossary

- Bone Marrow-organ in the body which makes blood cells. These cells are white cells, red cells and platelets.
  - Analogy: Bone marrow = garden

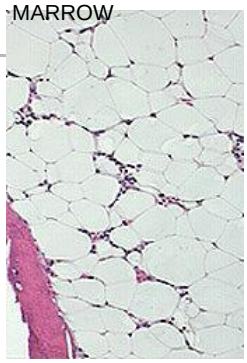
Glossary

- Hematopoietic Progenitor Cell (the old blood stem cell)-the seed cells that germinate into the blood cell flowers.
  - HPCs are harvested from: Bone Marrow, Cord Blood, Peripheral Blood Progenitor Cells.
  - All three sources can be manipulated to remove or enrich cells.
    - T-cell depletion, stem cell expansion

HEALTHY BONE MARROW



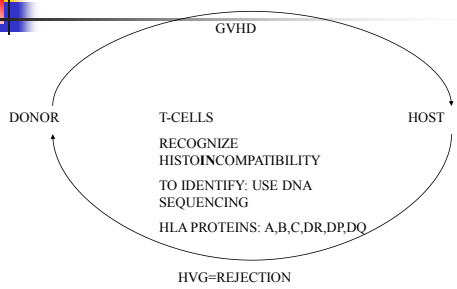
APLASTIC BONE MARROW



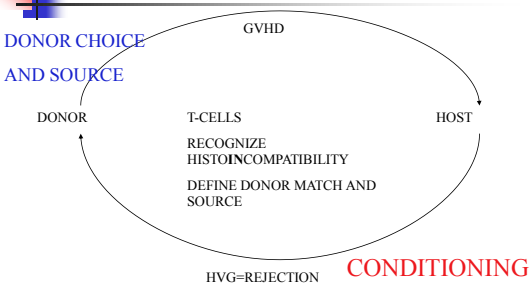
Glossary: Three Phases of Transplant

- Conditioning Phase: Chemotherapy +/- Radiation Therapy to condition the body to accept the transplanted cells.
- HPC infusion Phase: The actual infusion of HPC cells (usually through an IV…just like any blood transfusion). The ultimate in blood transfusions!
- Deal with it Phase: Side effects

The BMT Cycle



The BMT Cycle



What are the side effects?

- Day 0-Day 30
- Day 30-100
- Day 100-1 year
- Late Effects

SHORT TERM SIDE EFFECTS

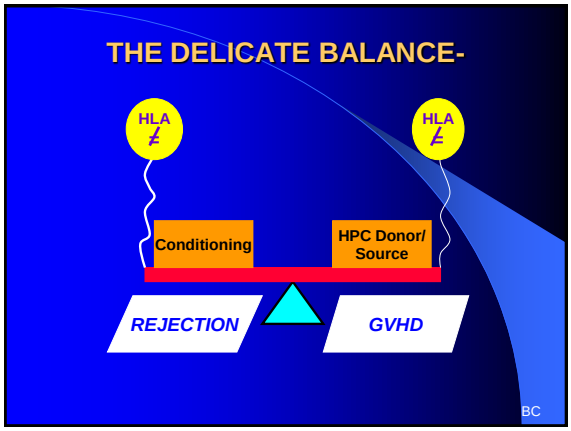
- Infection/Infection/Infection
  - Add Virus' to what you are used to.
- End Organ Toxicity
  - Lungs/Liver/Kidneys
- Acute GVHD
- Rejection

"Middle Term" Side Effects

- Graft Versus Host Disease and effects due to treatment for GVHD
- End-Organ Toxicity

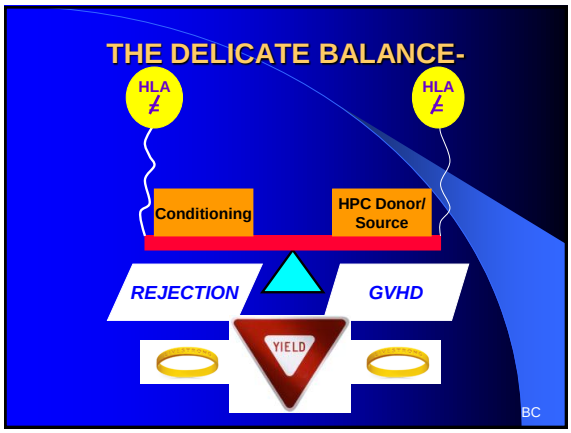
Late Effects

- Intensity of Treatment and chronic GVHD are the key variables.
  - Chronic GVHD is the main prognostic factor for quality of life and other late effects
- Fertility
- Growth and Development
- Late Cancers



Survivorship

- Lance Armstrong Foundation (LAF) defines cancer survivorship as living "with", "through" and "beyond" cancer (SAA).



What have we learned from historical (pre 2000) alternative donor data?

- We need an alternative donor transplant regimen that:
  - Prevents rejection
  - Prevents GVHD
  - Prevents late effects
  - Has excellent long term survival
  - ☺☺☺☺☺☺☺☺☺
- Deeg et al. and Bacigalupo et al. opened the era of improving outcomes with less intense regimens.
- Increasing numbers of publications with increasing options for conditioning and HPC source.

The "De-escalating TBI" Experience
Deeg et al. BBMT 2001

- 1994-1999; 14 centers
- N=50
- Median age=14 years (1-46y)
- Median Duration of SAA=14 months (3 months-264 months)
- Cyclophosphamide 200 mg/kg and ATG (equine) 90 mg/kg with de-escalation of TBI (3x200cGy; 2x200; 1x200)
- MTX/CSA GVHD prevention

The "De-escalating TBI" Experience
Deeg et al. BBMT 2001

- Survival was 58% at two years.
- Shorter disease duration and younger age improved survival.
- Unexpectedly high rate of diffuse alveolar damage.
- Data is the basis for current North American CTN trial:
  - Cyclophosphamide de-escalation trial.
  - Fludarabine/ATG/TBI 200 and de-escalating cyclophosphamide starting at 150 mg/kg total CY

The EBMT Experience
Bacigalupo et al. BMT 2005

- 1998-2004, 13 centers
- N=38
- Median age=14 years (3-37y)
- Median Duration of SAA=20 months (6 weeks-10 years)
- Fludarabine 30 mg/m2 x 3; CY 10 mg/kg x 4; Thymoglobulin 3.75 mg/kg x 4
- Low dose MTX/CSA GVHD prevention

The EBMT Experience
Bacigalupo et al. BMT 2005

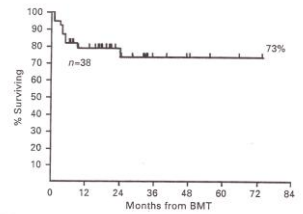


Figure 1 Actuarial survival of 38 patients with acquired SAA undergoing alternative donor transplants.

- Overall survival is 73%
- 7 cases of graft rejection or graft failure (5 alive)
- aGVHD II-III in 11%
- cGVHD in 27%
- Deaths were due to graft failure, EBV-PTLD, hemorrhage.

The EBMT Experience
Bacigalupo et al. BMT 2005

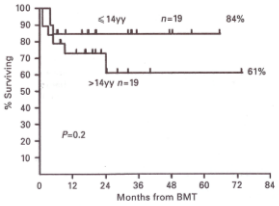
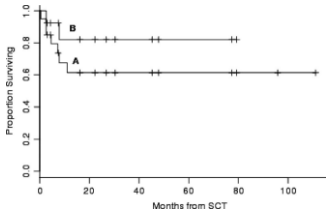


Figure 2 Actuarial survival of patients stratified according to age: there is a trend for improved outcome in patients aged ⩽14 years (84%) as compared to patients aged >14 years (61%).

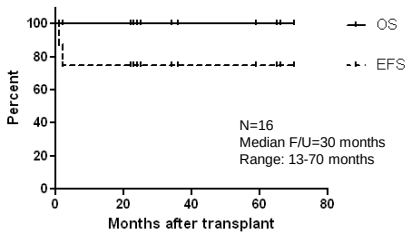
- Excellent survival without any TBI in the younger cohort.
- EBMT current trial uses a similar regimen with 200 cGy TBI to try to promote engraftment for those over the age of 14 years.

EBMT Approach Repeats

- MD Anderson Group
- Total of 20 patients, 13 treated per EBMT (B).
- Mixture of matched related donors and unrelated donors.
- Median age 34 years
- Leukemia and Lymphoma 2011



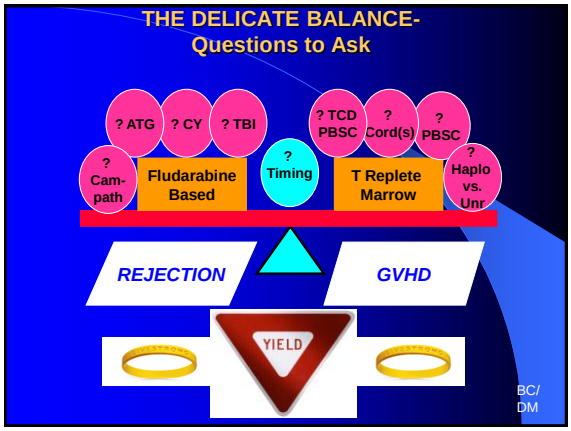
Comparison of event-free survival and overall survival in patients transplanted for Severe Aplastic Anemia: The Milwaukee Experience (2005-2011)



Unpublished Data

What did we learn from those studies?

- Less intense conditioning paired with matched related bone marrow improved compared to the papers from the mid 1990's.
- Rejection a primary reason for failure.
- Immune reconstitution (re-forming your immune system to fight infections) also a concern.
- Leads us to more research/questions.



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Can we improve outcomes using a different package?

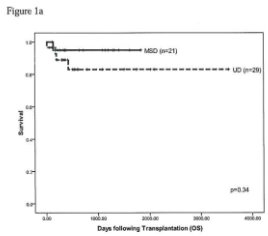
- Alemtuzumab (Campath) is a different antibody based treatment.
- Targets a different protein than ATG does.
  - CD52 (Alemtuzumab) vs. CD3 (ATG)
- Pioneered in Britain.
- Marsh et al: Alemtuzumab with Fludarabine and Cyclophosphamide..
- Blood 2011 (online publication)

Marsh et al 2011

- N=50 patients
  - 8-62 years age range (median age 35 years)
  - ¼ over the age of 50
- 21 Patients with HLA matched donor
- 29 patients with UNR donor (all except two 10/10 donors)

Marsh et al 2011

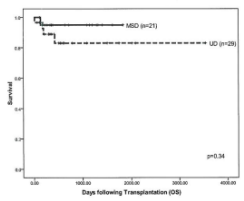
- Overall survival for the entire cohort comparing matched sibling donors with unrelated donors.
- Deaths due to chronic GVHD, invasive fungal infection at day 14, graft failure in two patients, and EBV PTLD in one.



Marsh et al 2011

- Overall survival for the entire cohort comparing matched sibling donors with unrelated donors.
- Six graft failures (2 died, 2 recovered, two retransplanted and alive)
- GVHD:
  - Acute GVHD in 15% (all grade I or II)
  - 7% cGVHD

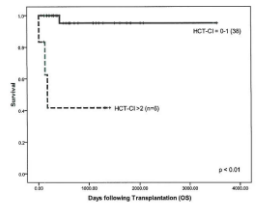
Figure 1a



Marsh et al 2011

- Overall survival for the entire cohort stratified by comorbidity index. (95% vs. 42% statistically significant)
- Concept of going to BMT when you are "well".

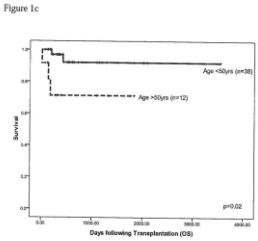
Figure 1b



Marsh et al 2011

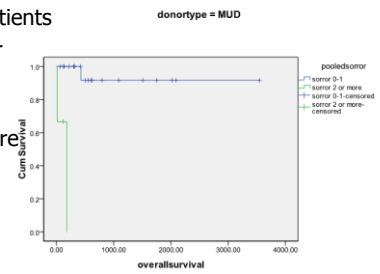
- Overall survival for the entire cohort stratified by age.

Figure 1c



Unrelated Donors and Patient Severity Score: TIMING, TIMING, TIMING (Unpublished Data from Dr. Marsh)

- Data for 23 patients
- 20 were Sorrer Score 0-1
- 3 had Sorrer Score of 2 or more



Marsh Take Home Messages

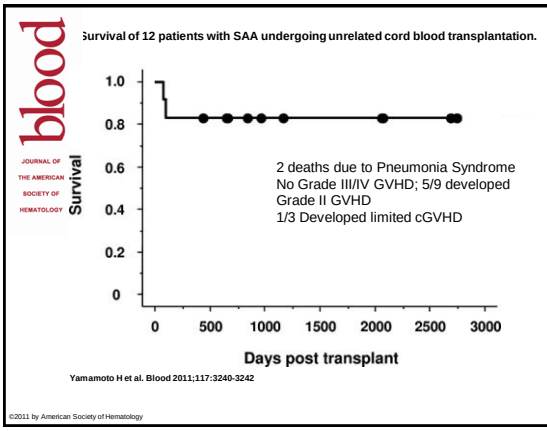
- Excellent Results with a primarily adult cohort.
- No use of Radiation.
- Chemotherapy dosing very favorable from a late effects profile.
- Data showing the healthier you are, the better your outcome.
  - Timing, Timing, Timing

Can we use cord blood as an HPC source?

- Cord Blood is an HPC source that has proven to be very useful for patients with malignant disease.
- In theory and in practice, may be associated with less GVHD for similar HLA matching.
- Engraftment has historically been a concern for patients with non-malignant diseases including SAA.

Yamamoto et al. Blood 2011

- 12 Adult patients with SAA
- 2002-2009
- Median Age: 49 years old.
- All "single cord" blood transplants.
  - Median Cell dose 2.5e7/kg
- Fludarabine/Melphalan/4 Gy TBI is the conditioning regimen.



Adult Cord Blood Take Home Messages

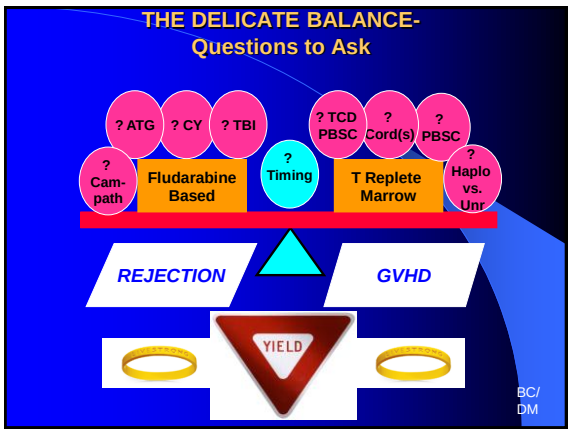
- Small numbers
- It is feasible with better outcomes than historical data
- Regimen published is somewhat intense.
- Cord Blood is an option to discuss with your transplanter.

Recent Data Observations

- Many choices for conditioning regimens.
- Increased choices for HPC source and donor.
- There are increased options for *non-transplant* options which can affect the crucial timing issue.

Questions to Discuss with MD

- Donor Options based on HLA typing
- Conditioning options based on donor options
- Timing Issues
  - Not too early, Not too late….JUST RIGHT



It's a Brave New World

- Special Issues for the new age of cord blood banking and in vitro fertilization.
- Very common questions now in the pediatric setting.

Interesting Case

- 3 year old girl with newly diagnosed SAA
- 3 siblings, no HLA match
- Plan to use Immune Suppression Treatment
- FAMILY HAD SAVED HER OWN CORD BLOOD: SHOULD WE USE IT?

FAMILY HAD SAVED HER OWN CORD BLOOD: SHOULD WE USE IT?

- Case report in the literature from Mt. Sinai in NY (Fruchtman et al. BBMT 2004)
- ATG/CSA/Pred followed by Cord Infusion
- Unclear on prolonged follow up

Preimplantation Genetic Diagnosis

- Uses In Vitro Fertilization (IVF) to find an HLA matched sibling.
- Following IVF, preimplantation genetic diagnosis (PGD) can be used for the purpose of HLA matching.
- This is done by selecting for and transferring only the embryos that are HLA matched to the affected child.

Preimplantation Genetic Diagnosis

- What is the role of preimplantation genetic diagnosis/in-vitro fertilization going to be for this disease?
- What is the best regimen to use if a matched sibling arrives at a later date using this technology?
  - Use of Fludarabine to help prevent rejection in a a heavily transfused patient.

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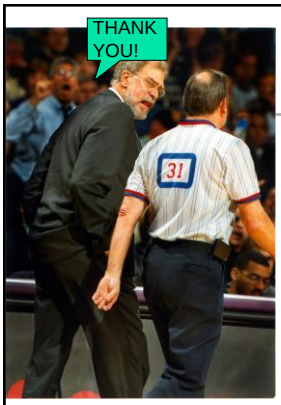

- AAMDS FOUNDATION
- Our patients and families
- Our team in Milwaukee
- dam@mcw.edu
- OPEN TIME FOR QUESTIONS
  - For personal questions, I recommend the afternoon session!