

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

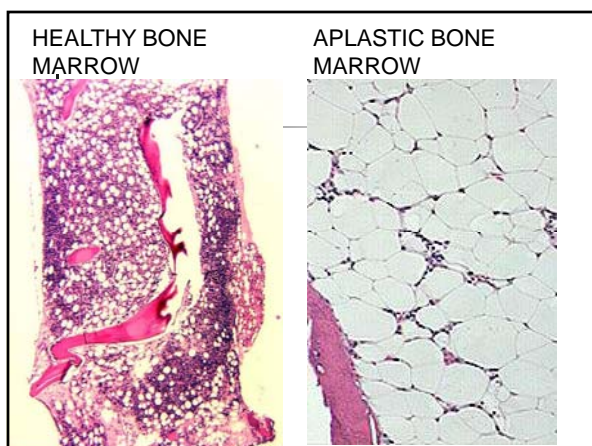
- Basic Concepts of Bone Marrow Transplantation
 - Teach you the language of BMT
 - Describe the process of BMT
 - Empower you to ask the right questions
- Review of Recent Data for outcomes for children and adults
 - Short term and long term data
- Answer Questions (if possible, avoiding personal questions)

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

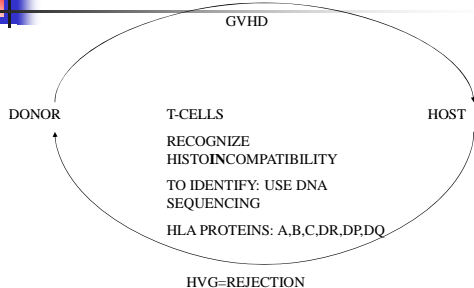
- Hematopoietic Progenitor Cell (the old blood stem cell)-the seed cells that germinate into the blood cell flowers.
 - HPCs are harvested from: Bone Marrow, Cord Blood, Peripheral Blood Progenitor Cells.
 - All three sources can be manipulated to remove or enrich cells.
 - T-cell depletion, stem cell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



Glossary: Three Phases of Transplant

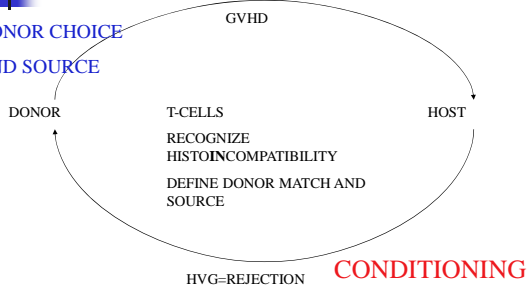
- Conditioning Phase: Chemotherapy +/- Radiation Therapy to condition the body to accept the transplanted cells.
- HPC infusion Phase: The actual infusion of HPC cells (usually through an IV...just like any blood transfusion). The ultimate in blood transfusions!
- Deal with it Phase: Side effects


The BMT Cycle



The BMT Cycle


DONOR CHOICE
AND SOURCE






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

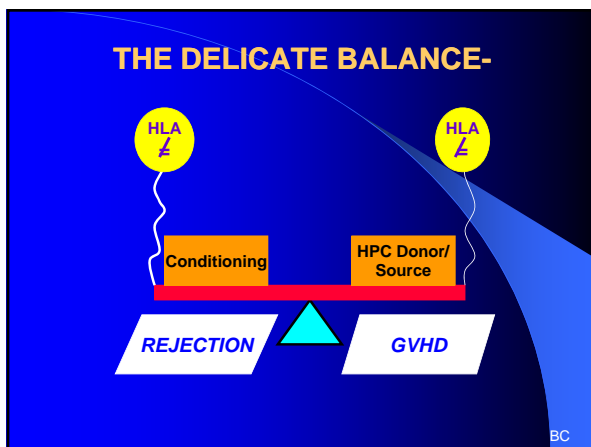


"Middle Term" Side Effects

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


Late Effects

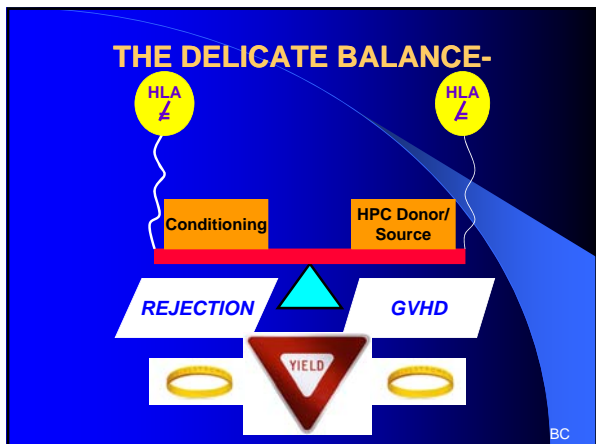
- Intensity of Treatment and chronic GVHD are the key variables.
 - Chronic GVHD is the main prognostic factor for quality of life and other late effects
- Fertility
- Growth and Development
- Late Cancers



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?

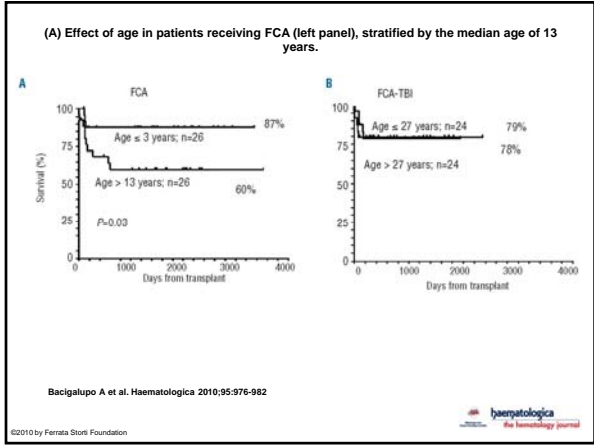
- We need an alternative donor transplant regimen that:
 - Prevents rejection
 - Prevents GVHD
 - Prevents late effects
 - Has excellent long term survival
 - 😊😊😊😊😊😊😊😊
- Increasing numbers of publications with increasing options for conditioning and HPC source.

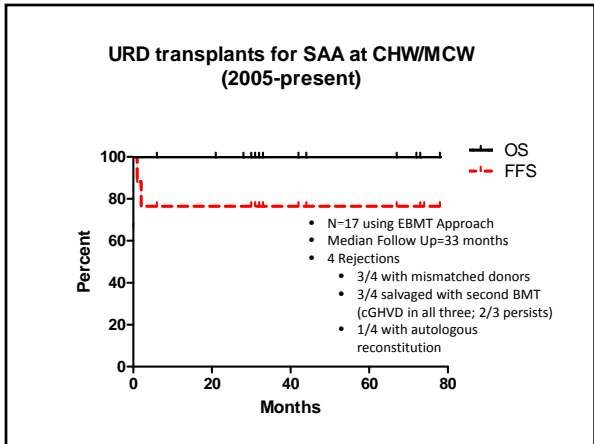
Well Matched UNR donor BMT

- Significant improvements in outcomes in the last 10 years reproduced in North America, Europe, and Asia.
- Common themes include the use of Fludarabine and Cyclophosphamide in the conditioning regimen and bone marrow as the HPC source
- TBI dose eliminated or low

The EBMT Experience Bacigalupo et al. BMT 2005

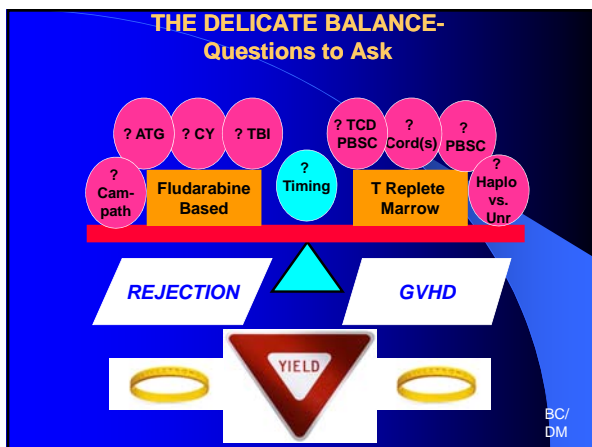
- 1998-2004, 13 centers
- N=38
- Median age=14 years (3-37y)
- Median Duration of SAA=20 months (6 weeks-10 years)
- Fludarabine 30 mg/m² x 3; CY 10 mg/kg x 4; Thymoglobulin 3.75 mg/kg x 4
- Low dose MTX/CSA GVHD prevention





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



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

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.

Figure 1a

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".

Marsh et al 2011

- Overall survival for the entire cohort stratified by age.


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

- Data for 23 patients
- 20 were Sorror Score 0-1
- 3 had Sorror 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



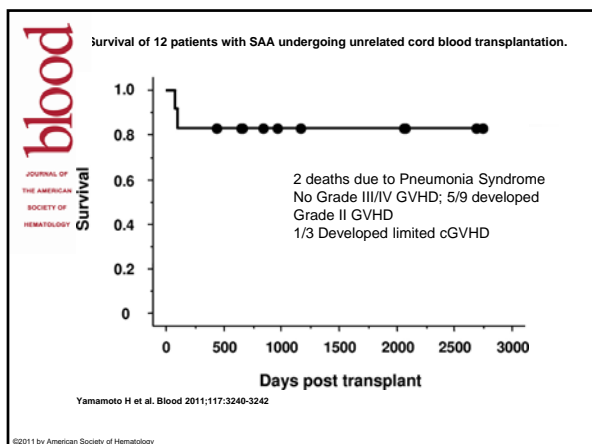
Can we use cord blood as an HPC source?

- 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.




Combined Haploidentical/UNR Cord Experience

- NHLBI data presented at ASH 2011
- N=8 (ages 9-20 years)
- CY 120/Flu125mg/m²/ATG 160/200cGY TBI
- Single 4/6 Cord PLUS CD34 Selected Haplograft


Combined Haploidentical/UNR Cord Experience

- All engrafted by day 42 (median day ANC>500 was day 10)
- 2 patients developed Grade II aGVHD
- 1 patient developed limited
- At ASH report 7/8 survive (median time of follow up 9 months)
 - One death due to CMV pneumonia.
- All survivors transfusion independent




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 transplant.



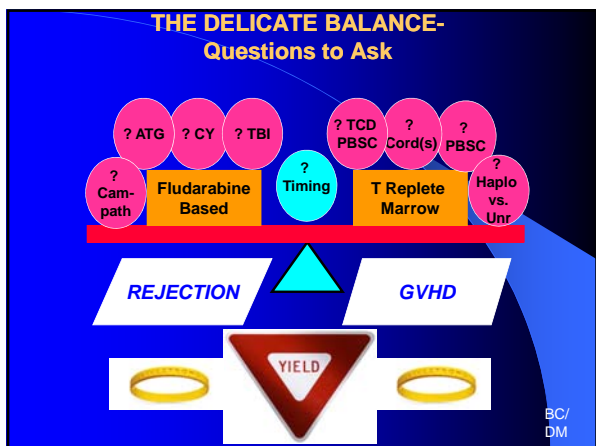
Recent Data Observations

- 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 heavily transfused patient.

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- AAMDS FOUNDATION
- Our patients and families
- Our team in Milwaukee
- dam@mcw.edu
- OPEN TIME FOR QUESTIONS
