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

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The BMT Cycle

DONOR

T-CELLS

RECOGNIZE

HISTOINCOMPATIBILITY

TO IDENTIFY: USE DNA SEQUENCING

HLA PROTEINS: A,B,C,DR,DP,DQ

HVG=REJECTION

HOST

GVHD
The BMT Cycle

DONOR CHOICE AND SOURCE

DONOR

T-CELLS
RECOGNIZE HISTOINCOMPATIBILITY
DEFINE DONOR MATCH AND SOURCE

GVHD

HOST

HVG=REJECTION

CONDITIONING

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).

THE DELICATE BALANCE -

- Conditioning
- HPC Donor/Source
- REJECTION
- GVHD
- YIELD
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
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

- 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

- 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)

N=16
Median F/U=30 months
Range: 13-70 months

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.

THE DELICATE BALANCE - Questions to Ask

- ? ATG
- ? CY
- ? TBI
- ? Fludarabine Based
- ? Timing
- ? T Replete Marrow
- ? TCD
- ? PBSC
- ? Cord(s)
- ? PBSC
- ? Cam-path
- ? Cy
- ? TBI
- ? Cord(s)
- ? PBSC
- ? Cam- path
- ? ATG
- ? Fludarabine Based
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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.
- 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)

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.
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

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 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.

Survival of 12 patients with SAA undergoing unrelated cord blood transplantation.

2 deaths due to Pneumonia Syndrome
No Grade III/IV GVHD; 5/9 developed Grade II GVHD
1/3 Developed limited cGVHD
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

THE DELICATE BALANCE - Questions to Ask

Fludarabine Based

? ATG

? CY

? TBI

? Cam-path

Timing

T Replete Marrow

? TCD

? PBSC

? Cord(s)

? PBSC

REJECTION

GVHD

YIELD

BC/ DM
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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THANK YOU!

• AA&MDS INTERNATIONAL FOUNDATION
  • Our patients and families
  • Our team in Milwaukee
  • dam@mcw.edu
  • OPEN TIME FOR QUESTIONS
    • For personal questions, I recommend the afternoon session!