Disclosures

- I have nothing to disclose for this presentation

I like to Talk.....
Especially about things I am passionate about!
I am a NY Yankee Fan!

Objectives

Improve your understanding of blood stem cell transplantation for bone marrow failure syndromes

Before....
During....
After the procedure

Objectives

- Introduce the concept of hematopoietic (blood) stem cells
- Location of blood stem cells and how they are collected
- Overview of blood stem cell transplantation
- Review existing barriers to successful outcomes
- Highlight advances made to HSCT procedure at JHU
- Identify challenges faced by long-term HSCT survivors

Stem Cells: Two Key Features

"Grandma" Cell
"Self replication"

Not all “Stem Cells” are Created Equal

Placenta (umbilical cord)
Bone marrow

"Hematopoietic" (Blood)
"Mesenchymal" (non-blood)
Stem Cells: Broad Therapeutic Potential

Blood Stem Cell Transplantation

Location

Source: BM space, blood, placental (cord blood)

Appearance

Healthy bone marrow

Auto vs. Allo

• "Autologous": Stem cells are collected from the patient, cryo-preserved and later re-infused after high-dose chemo.
• “Allogeneic”: The transplant of blood stem cells from someone other than self
  • Have to be “matched”
    - Sibling or other family member
    - Unrelated “volunteer” donor
    - "Be the Match" registry
    - one of many Cord Blood Registries

Collection

3 methods to obtain cells
• Bone Marrow Harvest
  – Stem cells obtained from pelvis (iliac crests)
  – Completed in OR
  – Donor requires anesthesia
  – “Juiciness” is operator dependent
Method #2

- **Peripheral Blood Stem Cells**
  - Mobilize stem cells from BM (G-CSF)
  - Cells are collected in peripheral blood
  - Leukopheresis procedure
  - Donor does not require anesthesia

Method #3

- **Cord Blood Stem Cells**
  - Placenta is enriched in primitive stem cells
  - Relative immaturity of immune system at birth results in lower rates of GVHD following transplantation
  - Can be collected without danger to mother and infant, frozen and stored
  - Ready to go (less time needed to arrange collection)

Terminology

- Stem cell transplantation (SCT)
- Bone marrow transplantation (BMT)
- Peripheral blood stem cell transplantation (PBSCT)
- Cord blood transplantation (CBT)
- Hematopoietic cell transplantation (HCT)
- **Blood stem cell transplantation**

True or False?

Blood stem cell transplantation is a new and highly experimental therapy that should be used only as a therapy of last resort.

FALSE!
Adults

**Best Source?**

NMDP Transplants by Cell Source

<table>
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<tr>
<th>Bone Marrow</th>
<th>Peripheral Blood Stem Cells</th>
<th>Cord Blood</th>
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**Application**

Aplastic Anemia: “Workers on Strike”

Healthy Unhealthy

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**Application**

Leukemia: “Hostile take over”

Leukemia Cells

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**Application**

“Defective products”: Myelodysplastic Syndrome (MDS)

- Stem cell defect
- Production of defective blood cell components
- Results in lowering of blood counts causing anemia, and increased risk of bleeding and infection
- Predisposition to leukemia
- Blood stem cell transplantation is only known cure

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**Application**

“Defective products”: Sickle Cell Anemia / Thalassemia

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**Application**

“Defective products”: Chronic Granulomatous Disease

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**Application**

- For high risk liquid and solid malignancies
- To replace a bone marrow that does not work
- To replace a bone marrow that makes defective products
  - Sickle cell anemia, Thalassemia
  - Chronic Granulomatous Disease (CGD)
- To replace a dysfunctional immune system (genetic disease)
  - SCID
  - Wiskott-Aldrich syndrome
  - Hemophagocytic lymphohistiocytosis (HLH)
- To replace an absent enzyme: Metabolic Disorders
  - Hurler’s Syndrome
  - Adrenal-leukodystrophy

**Procedure**

Chemo ± irradiation

Donor Stem cells

**Time Line**

GVH Prophylaxis (day –3 to day 180)

**The Balance**

![HLA](image.png)

**Conditioning**

HPC Donor/ Source

REJECTION

GVHD

**Unique Aspects**

“HSCT is not simply a procedure”

- Procedure itself is rather “lack luster”
- Coordination of comprehensive, specialized care is critical
days, weeks, months and years after HSCT
- Experience in transplant-related complications
  - Graft-vs.-Host Disease (GVHD)
  - Acute and chronic lung injury
  - Immune reconstitution and infection
  - Survivorship / late effects
- Ongoing cutting edge research

**BMT for AA+MDS**

- Donor availability
  - Match grade
  - related vs. unrelated
- Patient age
- Timing
  - Upfront vs. after IST
  - Minimize risk of infection / allo-immunization
- Type of BMT conditioning
  - with or without irradiation
- Stem cell source?
  - BM vs. peripheral blood vs. cord blood
Optimization of Therapy for Severe Aplastic Anemia
Based on Clinical, Biologic, and Treatment Response
Parameters: Conclusions of an International Working
Group on Severe Aplastic Anemia Convened by the
Blood and Marrow Transplant Clinical Trials
Network, March 2010

Michael A. Palese,1 Naot S. Young,2 Jakub Telila,3
Antoinette M. Rokos,1 H. Jacqueline Doug1, Paul Andreeff,1, Rupika Cobelo,1 Sagi Kupina,1
Mary Espinet,1 Richard Harms,1 Philip Schindler,5 Shivesh S. Aaron,2
Janelle F. Massipenis,1 Ranjan K. Dua,1 Nancy D'Antoni,1
Mary M. Holianska,1 Joseph H. Appel1,1

Adverse effect

Peripheral count recovery
Disease relapse
Clonal disease/progression
Chronic GvHD
Toxicities

HSCT
Complete
Rare
Rare (-3%)
10-40%
Endocrine, renal
VOD, cataracts
Pulmonary, SMN

IST
Incomplete
- 40% 
- 15-30%
None
Serum sickness
Acute reactions

Outcomes: MRD

Survival of Marrow Recipients
with All Preparative Regimens
1998–2006

Age < 18 Years  (n = 218)
Severe Aplastic Anemia

Survival

Log-rank p-value  = 0.12

Burroughs et al, FRCRC BJH 2012
Outcomes MUD

Comparative Outcomes of Matched-Related and Alternative Donor Stem Cell Transplantation for Pediatric Severe Aplastic Anemia

- 36 consecutive patients
- 15 pts. MRD
- 21 pts. AD
- 7 MUD
- 3 mMRD

Factors Contributing to Success of BMT for SAA

- Donor matching
- Conditioning Regimen
- Time to HSCT
- Recent advances

Obstacles

Barriers to success

- Regimen-related Toxicity (RRT)
  - Mucositis, lung, liver, kidney injury, infection
- Graft-vs-Host Disease (GVHD)
- Graft rejection / Failure
- Relapse of underlying malignancy
- Donor availability (related / unrelated)
- Challenges facing long-term BMT survivors
**RR Toxicity**

**Lung:** Early (acute) and Late (chronic)
Infectious vs. non-infectious
IPS frequently fatal

Liver inflammation
VOD, GVHD, infection, drug

Renal dysfunction:
AKI, TA-TMA

Mucositis

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**Graft-versus-Host Disease after HSCT**

- GVHD is a complex process
- Opposite to what occurs after a solid organ transplant
e.g. heart, liver, lung, kidney etc.
  - patient’s immune system rejects the donor “organ”
- GVHD: the donor stem cell “graft” rejects the host / patient
- Major complication of allogeneic BMT
  - Can be life threatening, major barrier to broadening scope of BMT
  - ALWAYS a risk unless donor and host are identical twins
  - Damage is caused by the donor immune system
  - Donor T lymphocytes recognize and reject foreign host tissue
  - Organs involved: skin, liver, intestine, LUNG
- Beneficial “Graft vs. Leukemia” (GVL) Effects

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**Goal: BMT**

Treatment strategies that reduce the damage of GVHD, facilitate the restoration of the blood and immune systems
AND preserve graft-vs-leukemia effects

**Minimize Late Effects!!**

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**Donor Availability**

Finding the “Perfect Match”

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The Dilemma

PROBABILITY OF HAVING A BONE MARROW DONOR

- No Donor
- Matched sibling (30%)
- Matched unrelated donor (10%)
- Unrelated cord blood unit (20%)
- Mismatched family donor (50%)

Crossing the HLA barrier

Donor Availability

Got Haplos?

Half-matched donors at JHU

Traditional matching

Patient

Dad

Mom

Siblings

25%

Patient

Dad

Mom

Siblings

25%

Patient

Dad

Mom

Siblings

83%
Haploidentical Transplants: Ablative or Nonablative

- **T-depleted BMT**
  - GvHD: High frequency of donor alloreactive T-cells in unmanipulated grafts
  - Rejection: Residual recipient alloreactive T-cells which survive conditioning
  - High failure rates due to ≥ 30% NRM at 1 yr
    - GvHD
    - Opportunistic infections

Use of Post-Transplant Cytoxan to regulate graft-vs-host reactions after allogeneic HSCT

- Incorporation of PTCy to RIC regimen Flu/Cy/200TBI
- Treatment in outpatient department!

Elegance is in the simplicity

- Virtually everyone has a donor
- Affordable and Transportable
- Easy and comfortable to administer
- No need for sophisticated and costly cell processing
- Donor can be mobilized in a timely fashion
- Acceptable toxicity AND GVHD rates!

Haplos at JHU

- 1998: HaploBMT platform developed in mouse model
- 1999: Phase I/II clinical trial initiated
- 2001-2: Pre-clinical, clinical results published
- 2004: Completed phase I/II (n=63), launched extended phase II (n=220)
- 2006: Sickle cell anemia trial initiated
- 2011: National phase II trial published (n=50)
- 2012: National phase III trial initiated (n=410)

> 500 haplo transplants at Hopkins
> 300 in last four years alone!
The Question

Have haplos changed the standard?

Moving Forward

What’s Next?

The Future

Reduced intensity conditioning, Haplo-donors, PTCy

- Expand the scope of allo-HSCT to non-malignant Dz
  - Beta Thalassemia Major
  - Sickle Cell Anemia
  - Severe aplastic anemia: recurrent and upfront
  - Inherited disorders of the immune system

- Auto-immune disorders

- Tolerance induction for solid organ transplant
A Phase II Trial of Non-Myeloablative Conditioning and Transplantation of Partially HLA-Mismatched or HLA-matched Unrelated Bone Marrow for Patients with Severe Aplastic Anemia and Other Bone Marrow Failure Syndromes

Newly diagnosed patients

- Cy 14.5 mg/kg/day
- Fludarabine 30 mg/m²/day
- Tacrolimus

Protecting our Children’s Health after HSCT

Kenneth R. Cooke, MD
Director, Pediatric BMT Program

Objectives

1. Introduce the scope of problems related to long-term complications following BMT
2. Describe long-term complications that can develop including:
   - Organ toxicity
   - Susceptibility to infection, including late infection
   - Ovarian/gonadal failure, Thyroid dysfunction
   - Ocular and oral issues
   - Musculoskeletal
   - Relapse and secondary cancers

True or False?
Because pediatric based regimens are kinder and gentler, they have been associated with inferior outcomes when compared to adult regimens.

Once a pediatric patient is 2 years out from BMT, all of the patient’s medical problems are in their “rear view mirror.”

Long-term side effects after BMT can be a consequence of pre-BMT therapy, BMT conditioning regimens, graft-vs.-host disease, and effects of other medications used after BMT.

Discussion Points

- Have patient and family members HLA typed asap
- Request a visit with a BMT specialist
- If no family match, KNOW YOUR OPTIONS!
  “Be the match” and cord blood registries
  Studies using half-matched (haplo) family donors
- If starting IST
  understand approach to first and second line agents
  timing for follow-up, impact of iron overload
- If AYA patient, ask if specialists are available
  consider a pediatric program?

Optimizing Outcomes for Pediatric Patients after BMT

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Pre-discussion Questions
True or False?

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Survivorship

Reduced Mortality after Allogeneic Hematopoietic-Cell Transplantation
Ted A. Gooley, Ph.D., Jason W. Chan, M.D., Steven A. Piegari, M.D., M.P.H., Sarangita Hingorani, M.D., M.P.H., Mohamed L. Sorri, M.D., Michael Brodsky, M.D., Paul J. Martin, M.D., Brenda M. Sandmeyer, M.D., Korin A. Marr, M.D., Frederick R. Appelbaum, M.D., Ranier Storb, M.D., and George B. McDermott, M.D.

Survivorship

Improved Transplant Outcomes
Survival of Children (Age ≤ 18 years) with Acute Leukemia

Survivorship

The Problem

Severe chronic medical conditions
- Growth and development
  - Skeletal maturation
  - Sexual maturation
- Emotional and social maturation
- Intellectual development
- Sexual development

Knowledge Gaps

Chronic Health problems in Cancer Survivors
- Cancer survivor
  - Cardiovascular
  - Endocrine
  - Olfactory
  - Gastrointestinal
  - Musculoskeletal
  - Neurological
  - Pulmonary
- General population

Robison and Hudson, Nature Reviews Cancer January 2014

Figure 1. Late effects after HCT are a result of the interaction of pre-HCT exposures to chemotherapeutic, radiation, and surgery with the transplantation conditioning regimen, acute complications of transplantation, and long-term-specific complications, such as bone and chronic health problems in cancer survivors. Chronic health problems in cancer survivors results from complications related to the cancer and its treatment, including secondary malignancies and immune suppression, as well as comorbidities present before transplantation that are exacerbated by cancer and its treatment. These problems can also modify other survivor outcomes, such as higher rates of infections and mortality from late effects, a higher frequency of cardiovascular disease, and a higher risk of suicide. The diagram highlights the complex interactions between pre-existing chronic medical conditions and late effects of HCT, emphasizing the importance of comprehensive follow-up care and management interventions to improve outcomes. 

Robison and Hudson, Nature Reviews Cancer January 2014
**Awareness**

**Bone marrow Transplant 17: 1573-1584 (2011)**

**REPORT**

National Cancer Institute-National Heart, Lung and Blood Institute/Pediatric Blood and Marrow Transplant Consortium First International Consensus Conference on Late Effects After Pediatric Hematopoietic Cell Transplantation: Long-Term Organ Damage and Dysfunction

Michael L. Nieder,1, George B. McDonald,1 Alix Kired,1 Sangenta Hingorani,1,2 Sara H. Ammerman,1, Kenneth R. Cooke,1 Michael A. Rolphsten,3 K. Scott Baker,3

AA - MDS, Rockville, MD

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**The Future**

**Multi-disciplinary Team Approach**

- Bone Marrow Transplant team
  - Pediatric and Internal medicine
- Primary care physicians
- Nursing / advanced practitioners
- Coordinators / social workers
- Dentists / Oral surgeons
- Fertility experts
- Endocrinologists
- Target organ sub-specialists

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**Conclusions**

- BSCT remains a curative therapy for SAA
- Outcomes continue to improve: MRD and MUD
- MRD HSCT: treatment of choice for pts. < 40 yrs
- If no MRD, IST continues to improve as well
- Successful alternative donor HSCT
  - Haplo-identical donors, cord blood
- BMT survivors face unique challenges
  - Impact outcome
- Know your options → life is all about them!

AA - MDS, Rockville, MD

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Future Directions

- Improving outcomes using alternative donors
  MUD, CB units, mMUD, “haplo-Identical” donors
- Optimize conditioning regimens
  Reduce toxicity and long term side effects
- Advances in prevention and Tx of GVHD and RRT
- Optimizing IST
  Best ATG type
  New agents → High dose cytoxan, campath, Eltrombopag
  Identify measures to predict outcome

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Once a pediatric patient is 2 years out from BMT, all of the patient’s medical problems are in their “rear view mirror.”

Long-term side effects after BMT can be a consequence of pre-BMT therapy, BMT conditioning regimens, graft vs. host disease, and effects of other medications used after BMT.

Ken’s “Secrets to Success”

1. Remain Passionate and Committed
2. Embrace Teamwork and Camaraderie
3. Find a good Mentor and then be one!
4. Be too Good to be Ignored
5. Find your happy place
6. Raise the Standard

Outstanding clinical research = best clinical care

Acknowledgements

Sidney Kimmel Cancer Center @ Johns Hopkins
Blood and Marrow Transplantation Program
Our patients and their families
The Cooke Laboratory

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NCI / NHLBI
LLS, BWF, NMDP, RWJF
Meredith A Cowden and Stadler Foundations

Pediatric Oncology and BMT at Hopkins
“Prominent enough to create the standard, intimate enough to feel the difference!”

Thank You!