BROKEN BONE MARROW: ACQUIRED APLASTIC ANEMIA

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Disclosure Statement

- I have no industry relationships to disclose
- I will discuss off-label use of medications

- Case studies have no individually identifiable patient information; all names and pictures are for illustrative purposes only

Learning Outcomes

- Able to contrast appropriate therapies for newly diagnosed aplastic anemia and refractory or relapsed disease

First-Line Therapies

Hematopoietic Stem Cell Transplant (HSCT)
Immunosuppressive Therapy (IST)

Foundation

- >70% mortality (infection/hemorrhage) within 1 year of diagnosis if only receive supportive care (transfusions, antibiotics)
- Newly diagnosed patients
  - Expedited HLA typing of patient and immediate family
  - Rule out other causes of bone marrow failure
  - Minimize transfusions
  - Aggressively treat infections

Treatment

- Goals of therapy
  - Ablation of ongoing auto-immunity
  - Replacement of deficient or abnormal HSCs
- Options
  - Hematopoietic stem cell transplant (HSCT)
  - Immunosuppressive therapy (IST)
- Considerations
  - Extent and duration of response
  - Short- and long-term risks

Stem Cell Transplant

Allogeneic HSCT with HLA-Matched Sibling Donor (MSD)

HSCT Overview

- Curative for AA
  - Potently immunosuppressive
  - Replaces absent/abnormal HSCs
- Risks
  - Graft failure or relapse
  - cGVHD (higher in non-Caucasians, older age)
  - Infection (especially if prolonged immune suppression for cGVHD)

MSD HSCT

- Preparative regimen: Cy/ATG (no TBI)
- GVHD prophylaxis: CSA and MTX
- Survival related to recipient's age: 80-90% if <20 years; only 70% if >20 years
- Graft failure: usually minimal; possibly due to fewer transfusions prior to HSCT
- BMT (marrow) transplant has better survival/less GVHD than PBSCT (peripheral blood) transplant

MSD HSCT

- Most children grow and develop normally and retain fertility
- In contrast, URD HSCT late effects include
  - Gonadal dysfunction
  - Growth disturbance
  - Avascular necrosis
  - Hypothyroidism
  - Cataracts

Immunosuppressive Therapy

IST Overview

- Reduces or eliminates aberrant immune process
  - Improves blood counts; though may have only a partial rather than complete response
  - First-line treatment if no matched sibling donor
- Risks
  - Relapse/recurrence of pancytopenia
  - ~10% risk of malignant clonal evolution (PNH, MDS, AML; especially monosomy 7) which may occur late (>10 years from initial treatment)

Anti-Thymocyte Globulin (ATG)

- Horse, rabbit or porcine derived antibodies that react against human T-cells
- Lymphocytotoxic and immunomodulatory
- Horse ATG (hATG) vs rabbit ATG (rATG)
  - hATG has better hematologic response and survival than rATG
  - No different in relapse or clonal evoluation

Equine ATG (hATG)

- 40 mg/kg IV over 4-6 hours daily x4 days
- Anaphylaxis: manufacture recommends skin test prior to first dose
- Infusion-related toxicity (fever, hives and chills): pre-medication with prednisone, acetaminophen and diphenhydramine
- Serum sickness (fever, rash, joint muscle aches): prednisone taper day 5-14
- PPI for GERD prophylaxis

Cyclosporine

- Non-steroidal immunosuppressive agent
- Inhibits T-cell function by targeting and suppressing T-cell proliferation and activation
- 5-15 mg/kg/day ÷ BID/TID
- Target CSA level: 200-400 (150-250 if toxicity)
- NOTE: Different ways to measure level
- Treat for 6-12 months after stable remission (?)
- Slow taper over 6-18 months (?)

CSA Considerations

- Hypertension: amlodipine preferred agent
- Gingival hyperplasia: short course azithromycin
- Monitor renal function (creatinine)
  - Adequate hydration
  - Avoid other nephrotoxic drugs
- Neurotoxicity (tremor, headache, seizure)
- Hirsutism
- Opportunistic infections

IST in Pediatric Aplastic Anemia

	NIH (Scheinberg, 2008)	NAPAAC (Rogers, 2019)
Study years	1989-2006	2002-2015
Number of patients	77	264
Response rate at 6 months Overall response rate	75% (26% CR)	49% (21%CR/20%VGPR) 71%
Relapse rate	33% at 10 years	16% at 5 years, no plateau
Clonal evaluation	8.5% (MDS); leukemia: 0%	MDS/leukemia: 1.9% Acquired abnormalities: 7%
Overall survival	80% at 10 years; 90% in children who responded	93% at 5 years

IST: hATG/CSA

- ~75% have partial or complete response
  - Response may take more than 6 months
  - Children are more likely to have a complete response than adults
- ~30% of responders will relapse
- ~5-10% lifetime risk of clonal evolution; most occur within 2-4 years
- So ~50% of children who receive IST ultimately require additional therapy

Can We Improve IST?

- Adding agents to hATG/CSA (MMF, sirolimus, growth factors) has not improved response, relapse, clonal evolution, or overall survival
- Eltrombopag (Promacta) showed promising initial data in adults, but on recent study did not provide any obvious therapeutic benefit to pediatric patients with SAA (Groarke, 2019)
- Data on high dose cyclophosphamide is conflicting

IST vs MURD HSCT?

- IST
  - Long term survival is greater than 80%, better for responders
  - Risks: refractory, partial response, relapse, clonal evolution
- Matched unrelated donor (MURD) HSCT
  - Long-term *survival* is improving; similar to MSD on recent studies
  - Risks: graft rejection, GVHD, infections, late effects TBI/alkylating agents (optimal conditioning regimen TBD)

TransIT Study*: IST vs MURD

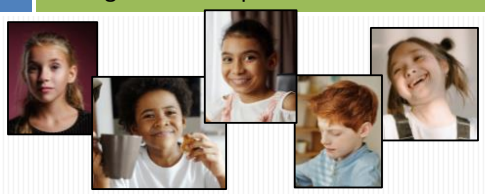
- Unrelated Donor **Trans**plant Versus **I**mmune **T**herapy in Pediatric Severe Aplastic Anemia
- Transplant naïve, less than 25 years old
- Mandated testing for IBMFS (FA, DC; SDS)
- No suitable fully matched related donor
- At least two suitable (9/10 or 10/10) MURDs on NMDP search
- If randomized to HSCT, start preparative regimen within 6-8 weeks
- Feasibility study; timely evaluation and safety of up front MURD BMT

*ClinicalTrials.gov Identifier: NCT02845596

Relapsed or Refractory Disease

- Treatment with HSCT (MURD, haplo-identical, cord blood) is superior to second course of IST (Rogers, 2019)
- Second course of IST should only be considered if
  - No appropriate donor
  - Not suitable for transplant (uncontrolled infection, organ toxicity, lack of social support)

Putting a Face on Aplastic Anemia



Charlotte

- 7-year-old Caucasian female
- Two-week history of easy bruising/petechial rash
- Isolated thrombocytopenia - presumed to have ITP, but not responsive to IVIG
- Serial CBCs showed progressive pancytopenia

Charlotte

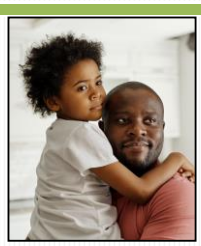
- CBC: Hgb 6.1, PLT 7K, ANC 0
- Bone marrow: profoundly hypocellular (<5%)
- Workup for IBMFS: negative
- Donor options: HLA-matched sister

MSD HSCT

- Conditioning: Cy/ATG (no TBI)
- GVHD prophylaxis: CSA, short course of MTX
- Engrafted: day 28
- GVHD: none
- Doing well at 4 years post-transplant

Jonah

- 3-year-old African-American male
- Moderate pancytopenia found during rheumatology work up for joint stiffness
- Serial CBCs showed progressive pancytopenia



Jonah

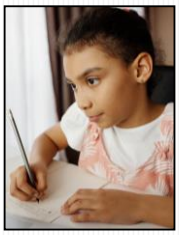
- CBC: Hgb 6.5, PLT 6K, ANC 340
- Bone marrow: profoundly hypocellular
- Workup for IBMFS: negative
- Donor options: several 9/10 DR-mismatched URDs
- Family declined participation in treatment studies

IST with hATG/CSA

- Treatment: IST
- Transfusion independent at 3 weeks
- Complete response at 6 months: Hgb 11.3, PLT 152K, ANC 2278
- Started slow CSA taper at 10 months and tapered off over 10 months
- Off therapy marrows: 45-70% cellularity; persistent mild macrocytosis (elevated MCV)
- Doing well at 4 years post-diagnosis

Darlene

- 7 year-old Hispanic female
- Two-week history of increased bruising/bleeding and SOB/lightheaded with activity



Darlene

- CBC: Hgb 4.3, PLT 6K, ANC 0
- Bone marrow: profoundly hypocellular (<5%)
- Workup for IBMFS: negative
- Donor options: two 9/10 A-mismatched URDs
- Family was interested in treatment studies, but both donors became unavailable

IST with hATG/CSA

- Treatment: IST
- Complications: none
- No response at 6 months
  - Transfusion dependent
  - ANC 100, but no documented infections
  - Persistently hypocellular marrow

Haploidentical HSCT for Refractory Disease

- Donor: mother
- Conditioning: Flu/Cy/ATG, 200 cGy TBI
- GVHD prophylaxis: post-transplant Cytoxan; tacrolimus, MMF
- Engrafted: Day 17
- GVHD: none
- Complications: bacteremia; psychogenic seizures
- Doing well at 295 days post-transplant

Wyatt

- 8-year-old Caucasian male
- 2-week history of easy bruising and fever

Wyatt

- CBC: Hgb 9, PLT 4K, ANC 50
- Bone marrow: profoundly hypocellular (<5%)
- Workup for IBMFS: negative
- Donor options: more than 10 fully matched URDs
- Family very interested in participating in treatment studies

IST + Eltrombopag

- Treatment: IST on the Novartis Oncology Clinical Trial Protocol CETB115E2201 (hATG/CSA + EPAG)
- Complications: unable to tolerate full dose study medication; multiple F&N admissions; pulmonary nodule concerning for fungus
- Poor response at 6 months
  - Transfusion dependent
  - ANC 500-1000
  - Persistently hypocellular marrow

MURD HSCT for Refractory Disease

- Donor: 10/10 MURD
- Conditioning: Flu/Cy/ATG, 200 cGy TBI
- GVHD prophylaxis: CSA, short course of MTX
- Engrafted: Day 27
- GVHD: none
- Complications: CSA-associated renal toxicity
- Doing well at 50 days post-transplant

Ruth

- 7-year-old Caucasian female
- 10-month history of easy bruising/ petechial rash

Ruth

- CBC: Hgb 4, PLT 7K, ANC 360
- Bone marrow: profoundly hypocellular (<5%)
- Workup for IBMFS: negative
- Donor options: more than 50 fully matched URDs

MURD on TransIT Trial

- Conditioning: Flu/Cy/ATG, 200 cGy TBI
- GVHD prophylaxis: CSA, short course of MTX
- Engrafted: Day 20
- GVHD: none
- Complications: AKI
- Doing well at 2 years post-transplant

Take Home Messages

- MSD BMT is treatment of choice with survival >90% and minimal complications
- IST with horse ATG/CSA is standard medical therapy for those lacking a related donor; 80% respond but complications include relapse and clonal evolution
- HSCT is treatment of choice for refractory/relapsed disease
- Research regarding alternative HSC sources, best conditioning regimen, and novel agents is needed

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THANK YOU!

Questions?